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THE INFLUENCE OF ANABOLIC STEROID (DELADUMONE) THERAPY ON THE CLINICAL AND METABOLIC ASPECTS OF PAGET'S DISEASE*

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In patients with Paget's disease (osteitis deformans), the presence of uninvolved healthy bone in a spotty distribution indicates that the nature of the initial pathologic disturbance in this osseous disorder is localized instead of generalized or systemic (1, 2). Evidence that the initial lesion is localized bone destruction has been presented elsewhere by one of us (ECR) (1). The consequences of the local lesion, however, usually are of sufficient magnitude to induce generalized alterations in calcium and osseous metabolism. For example, the destruction of bone frequently releases enough calcium to cause hypercalciuria, a tendency toward hypercalcemia, renal calculi, and/or metastatic calcification (1–3). Furthermore, the localized bone destruction, by weakening the involved portion of the skeleton so that it becomes more sensitive to the stresses and strains of weight-bearing, accelerates osteoblastic activity and as a consequence stimulates bone formation and repair in the involved area. This compensatory process is manifested by a rise in the level of serum alkaline phosphatase, which is an index of increased osteoblastic activity and hence of increased bone formation (1, 2).

In 1956, we began a study of patients with Paget's disease who exhibited systemic alterations of calcium and osseous metabolism, and the effect thereon of steroids known to have systemic anabolic influences on calcium and bone

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metabolism in man. The hormonal material chosen for the investigation was a preparation of androgen and estrogen in combination (Deladumone). Because of considerable difficulty in finding cases of Paget's disease with compensatory hypercalciuria who were suitable for metabolic balance studies, only 2 patients were investigated. The purpose of this communication is to present the data thus obtained concerning the effect of anabolic steroid therapy with Deladumone on the clinical and metabolic aspects of Paget's disease.

CLINICAL MATERIAL

Selection of Patients

From a fairly large group of patients with Paget's disease, 2 patients were selected who had: 1) marked osseous involvement as indicated by roentgenograms; 2) generalized alterations in calcium and osseous metabolism as indicated by an increased urinary excretion of calcium (165 and 152 mg. per twenty-four hours, respectively) and an elevated level of serum alkaline phosphatase (36 and 122 Bodansky units, respectively); and 3) relative freedom from other complicating medical conditions. The patients were chosen from the inmates of the Bird S. Coler Hospital and were investigated on the Metabolic Ward of the Metropolitan Medical Research Unit of that institution.

Case Histories of Selected Patients

Case 1

V. V., a 54-year-old woman, sought medical advice for backache eighteen years before admission; at that time she was found to have Paget's disease. The backache had persisted. Bowing of the left leg was noted ten years before admission; it was associated with pain in the left thigh. The patient experienced two falls; the first resulted in a fracture of the right patella, and the second in a break in the previously-placed patellar wiring. During the four years before admission, she had become increasingly deaf in the right ear. She had occasional headaches which were usually worse in the morning and always relieved by aspirin. Until one year before admission, she had been able to walk with a brace in spite of a severe deformity of the right leg and thigh; since then she had walked only with the aid of crutches. It was established that 3 sisters had Paget's disease, but there were no other known instances of the disease in her family.

Physical examination revealed a very thin woman, 64 inches tall, weighing 90 pounds, with a blood pressure of 110/70 mm. Hg, a pulse rate of 76 per minute, and a respiratory rate of 16 per minute. The salient physical findings included: 1) widening of the skull, most marked in the bitemporal diameter; 2) almost complete loss of hearing in the right ear; 3) severe dental caries; 4) marked kyphosis necessitating the wearing of a brace; 5) severe bowing and tenderness of the right tibia with considerable pain in the right leg, knee and thigh on attempted motion; and 6) bowing and shortening of the left thigh and leg in association with atrophy of the leg muscles.

Laboratory examination: On admission, the blood count and urinalysis findings were within normal limits. The level of serum total protein was 6.7 Gm. per 100 ml. In terms of mg. per 100 ml., other blood or serum concentrations were: sugar (fasting) 80, urea nitrogen 12.0, cholesterol 288, total calcium 9.9, and inorganic phosphorus 4.4. At the time of the metabolic balance study, the urinary calcium excretion was 149 mg. per twenty-four hours and the serum alkaline phosphatase level was 36 Bodansky units. Roentgenograms of the skeleton revealed extensive Paget's disease, with involvement (in order of decreasing severity) of the pelvis, the skull, the spinal column, both femurs, both tibias, and the right humerus.

Some of the results of hormonal therapy are presented in Table 1 and Figure 1.

Case 2

J. S., a 76-year-old man, had noted for several years that the size of his head was increasing. Although he had been admitted to the hospital for arteriosclerotic heart disease with left ventricular failure, at the time of the metabolic study there was no evidence of cardiac decompensation, and the findings were those of advanced Paget's disease with generalized arteriosclerosis and senile emphysema. The patient was almost totally deaf, but had not been so all of his life.

Physical examination on admission revealed an elderly man, 68 inches tall, weighing 137½ pounds, with a blood pressure of 125/65 mm. Hg, and a pulse rate of 75 per minute. The salient physical findings included: 1) a skull that was much enlarged in all dimensions with a particularly pronounced increase in the bitemporal diameter; 2) a thoracic cage somewhat fixed in the position of midrespiration and characteristic of pulmonary emphysema; 3) a high-pitched, fairly intense apical systolic murmur, not radiating in any particular direction; 4) marked anterolateral bowing of both legs; and 5) absence of the superficial and deep tendon reflexes bilaterally. No pathologic reflexes were present, and there was no apparent loss of sensory or motor power.

Many urinalyses were performed but the findings were always within normal limits. Repeated examinations of the sputum did not disclose any tubercle bacilli. On admission, the hemoglobin level was 11 Gm. per 100 ml.; white blood cell count, 8,150 per cu. mm.; carbon-dioxide combining power, 27.1 millimols per liter. The serum total protein level was 6.5 Gm. per 100 ml. In terms of mg. per 100 ml., other blood or serum findings were: sugar (fasting) 75, urea nitrogen 16.1, cholesterol 185, cholesterol esters 187, total calcium 9.3, and inorganic phosphorus 3.5. At the time of the metabolic balance study, the urinary calcium excretion was 180 mg. per twenty-four hours, and the serum alkaline phosphatase level was 122 Bodansky units. Roentgenograms of the bones revealed Paget's disease with classic areas of osseous destruction and repair in virtually every portion of the skeleton. The most advanced changes were noted in the cranium. There was involvement (in order of decreasing severity) of the lumbar spine, the pelvis, the femurs, the tibias, the ribs, the clavicles, the scapulas, and the upper and the lower bones of both arms.

Some of the results of hormonal therapy are presented in Tables 2 and 3 and Figures 2 and 3.

HORMONAL PREPARATIONS, PLAN OF STUDY AND METHODS

Anabolic steroid (Deladumone) medication. The anabolic hormonal medications consisted of two concentrations of a mixture of the long-acting injectable androgenic steroid ester, testosterone enanthate, with the long-acting injectable estrogenic steroid ester, estradiol valerate. One preparation, designated as Deladumone Regular (R) contained 90 mg. of testosterone enanthate and 4 mg. of estradiol valerate in each ml. of sesame oil. The other preparation, designated as Deladumone Special High Potency (SHP), contained 200 mg. of testosterone enanthate and 10 mg. of estradiol valerate in each ml. of sesame oil. The ratio of the two steroid esters in the Deladumone preparations had been demonstrated (on the basis of previous clinical studies) to provide a mixture of the androgen with the estrogen which was balanced so that there was a minimum of the undesirable effects of either hormone singly (masculinization or feminization) (4). The duration of action of a single injection of either of these preparations ranged from three to four weeks, dependent upon the response to be evaluated; there was a tendency for the duration of action to be four weeks or longer with the larger doses (4). Either preparation could be injected readily through a small-gauge needle; the injections (deep intramuscular) were well tolerated by the patients.

Anti-anabolic (corticosteroid) medication. In 1 patient (No. 2), ancillary studies were carried out in which 5-mg. tablets of prednisone were administered by mouth in a dosage of 30 mg. per day.

Plan of study

Metabolic balance regimens were started and the patients were studied for suitable periods of time before, during, and after single injections of the Deladumone preparations, or (in 1 case) during continuous medication for twenty-four days with prednisone tablets. Observations and measurements of the clinical, roentgenographic and biochemical status were made continuously or periodically throughout the control and treatment phases in order to assess the effect of the medications.

Methods

Intake. The patients were given diets with a constant daily intake of protein (1 Gm. per Kg. of body weight), calcium (900 mg.), phosphorus and calories. Fluids were permitted without restriction.

Excreta. The urine was collected continuously throughout the studies and analyzed in three-day pools for nitrogen, calcium and phosphorus. The excretion of these substances in the feces was not determined. In order to calculate the nitrogen balance, the excretion of nitrogen in the feces was assumed to be 1 Gm. per twenty-four hours. A positive nitrogen balance was assumed if the urinary nitrogen (Gm.) plus the assumed fecal nitrogen value of 1 Gm. was less than the calculated or measured nitrogen intake.

Other determinations. The clinical status of the patients was evaluated carefully each day. The serum levels of total calcium, inorganic phosphorus and alkaline phosphatase, and the body weight were determined at frequent intervals throughout the studies. Roentgenograms of the involved bones were also obtained frequently.

Activity. The physical activity of both patients had been markedly restricted for some months prior to the investigations. By supervision, it was maintained unchanged at approximately the same level throughout the studies.

Treatment regimens

Case 1—Deladumone. This patient underwent fifteen days of control observations prior to the first injection of anabolic steroid medication. She was given a single injection of 2 ml. of the Deladumone-SHP preparation on the sixteenth, fifty-eighth, eighty-eighth, and one hundred and forty-second days of the study. Observations were made continuously for one hundred and fifty-three days from the start of the initial control period.

Case 2—Deladumone. This patient was studied for twenty-four days under control conditions prior to medication. He was given a single injection of 2 ml. of the Deladumone-R preparation on the twenty-fifth day, and 2 ml. of the Deladumone-SHP preparation on the sixty-first day of the study. Observations were made continuously for one hundred and twenty days from the start of the initial control period.

Case 2—Prednisone. In order to compare the effects of anti-anabolic (corticoid) steroid with those of anabolic steroids on calcium and osseous metabolism, this patient was given 30 mg. of prednisone by mouth daily for twenty-four days starting on the one hundred and twenty-first day after the beginning of the initial control period. This medication was discontinued on the one hundred and forty-fifth day. On the one hundred and forty-eighth day, the patient had an attack of fever associated with a mild pneumonitis, lasting three days; this may have induced a marked increase in endogenous corticosteroid production for several weeks. Observations were continued for one hundred and eighty days after the start of the prednisone therapy (for three hundred days from the start of the initial control period).

RESULTS OF DELADUMONE THERAPY

I. *Clinical Aspects*

In Case 1, the bone pain was not improved following the first injection (2 ml. of Deladumone-R), but with the second injection (2 ml. of Deladumone-SHP)

forty-two days later, the pain in the hips was almost entirely relieved and the patient felt stronger. The improvement was noted from the fifth to the twelfth days after the injection, after which the pain again became progressively worse and attained the former intensity within a few days. The same sequence of recession and reappearance of pain occurred following a third injection (2 ml. of Deladumone-SHP) thirty days after the second and seventy-two days after the first. It also occurred following a fourth injection (2 ml. of Deladumone-SHP) fifty-four days after the third, eighty-four days after the second, and one hundred and twenty-six days after the first injection. There was no significant gain in body weight after the first injection, but during the period of the subsequent three injections there was a gradual increase in weight, with a maximal gain of 3.0 Kg.

Patient J. S. (Case 2) had never complained of bone pain in spite of the severity of the osseous disease. Following the injections of Deladumone, there were no changes in his body weight or strength, or in the objective signs of the disease.

Neither patient experienced any masculinizing or feminizing effects as a result of the Deladumone therapy.

II. *Metabolic Aspects*

Urinary calcium excretion

In Case 1, the 24-hour urinary calcium excretion varied between 149 and 182 mg., with an average of 165 mg. during the fifteen days of preliminary control observations (Table 1 and Fig. 1). Following each of the four injections of 2 ml. of Deladumone-SHP there was a marked decrease in the amount of calcium excreted in the urine. The fall was apparent within six to nine days. The maximal 24-hour decrease of 40 to 76 mg. (30 to 45 per cent) below the average control values was reached nine to fifteen days after the injection. The excretion of calcium did not return to the pre-injection range until twenty-one to twenty-seven days after the administration of Deladumone. A "rebound" increase in calcium excretion to a level above the average for the control period occurred on the twenty-fourth to thirty-ninth days after the first injection, and on the forty-second to fifty-first days after the third injection; following the second and the fourth injections, observations were not made for a sufficient length of time to permit evaluation of "rebound" increases.

As shown in Figure 1, the third injection of Deladumone was given thirty days after the second dose, at a time when the urinary calcium excretion still was reduced as a result of the second injection. The fall in calcium excretion induced by the second dose was continued, and for a time was depressed further, by the third injection of the hormonal preparation; thus it required seventy-eight days for calcium excretion to rise to the level observed just before the second injection. The second and the third doses considered together, therefore, constitute effective and sustained maintenance therapy. The minor fluctuations in the consecutive three-day values probably represented lack of precision in collecting the urine in exactly 24-hour specimens.

In Case 2, the 24-hour urinary calcium excretion fluctuated between 127

TABLE 1

Effect of Deladumone on Urinary Calcium Excretion and Serum Alkaline Phosphatase Level in Paget's Disease

(Case 1: V. V., female, aged 54)

Days	Urinary Calcium (mg./24 hrs.)	Serum Alk. Phosphatase (Bod. units)	Difference From Control Periods: Urinary calcium (mg./24 hrs.)	Difference From Control Periods: Serum alk. phosphatase (Bod. units)
No Treatment (control periods for first injection)				
1–3	149	36	−16	0
4–6	164	—	−1	—
7–9	162	—	−3	—
10–12	168	—	+3	—
13–15	182	—	+17	—
Avge.	165	36		
*2 ml. Deladumone** (first injection)				
16–18	153	—	−12	—
19–21	159	54	−6	+18
22–24	89	—	−76	—
25–27	114	—	−51	—
28–30	109	—	−56	—
31–33	121	—	−44	—
34–36	153	—	−12	—
37–39	171	—	+6	—
40–42	184	80	+19	+44
43–45	184	—	+19	—
46–48	107	—	−58	—
49–51	169	—	+4	—
52–54	203	—	+38	—
55–57	143	30	−22	−6
No Treatment (control periods for second injection)				
43–45	184	—	+23	—
46–48	107	—	−54	—
49–51	169	—	+8	—
52–54	203	—	+42	—
55–57	143	30	−18	0
Avge.	161	30		
*2 ml. Deladumone** (second injection)				
58–60	147	—	−14	—
61–63	168	—	+7	—
64–66	144	—	−17	—
67–69	113	—	−48	—
70–72	130	—	−31	—
73–75	120	—	−41	—
76–78	115	—	−46	—
79–81	119	—	−42	—
82–84	148	—	−13	—
85–87	129	—	−32	—
No Treatment (control periods for third injection)				
82–84	148	—	+9	—
85–87	129	—	−10	—
Avge.	139	30†		
*2 ml. Deladumone** (third injection)				
88–90	132	—	−7	—
91–93	118	87	−21	+57
94–96	133	—	−6	—
97–99	113	—	−26	—
100–102	77	—	−62	—
103–105	117	—	−22	—
106–108	100	28	−39	−2
109–111	148	—	+9	—
112–114	125	—	−14	—
115–117	138	—	−1	—
118–120	142	—	+3	—
121–123	135	93	−4	+63
124–126	131	—	−8	—
127–129	140	—	+1	—
130–132	150	—	+11	—
133–135	136	20	−3	−10
136–138	160	—	+21	—
139–141	139	—	0	—
No Treatment (control periods for fourth injection)				
127–129	140	—	−5	—
130–132	150	—	+5	—
133–135	136	20	−9	0
136–138	160	—	+15	—
139–141	139	—	−6	—
Avge.	145	20		
*2 ml. Deladumone** (fourth injection)				
142–144	167	—	+22	—
145–147	139	—	−6	—
148–150	105	34	−40	+14
151–153	105	—	−40	—

* Special High Potency Deladumone (SHP) containing 200 mg. of testosterone enanthate and 10 mg. of estradiol valerate per ml. of sesame oil.

† Control value for second injection.

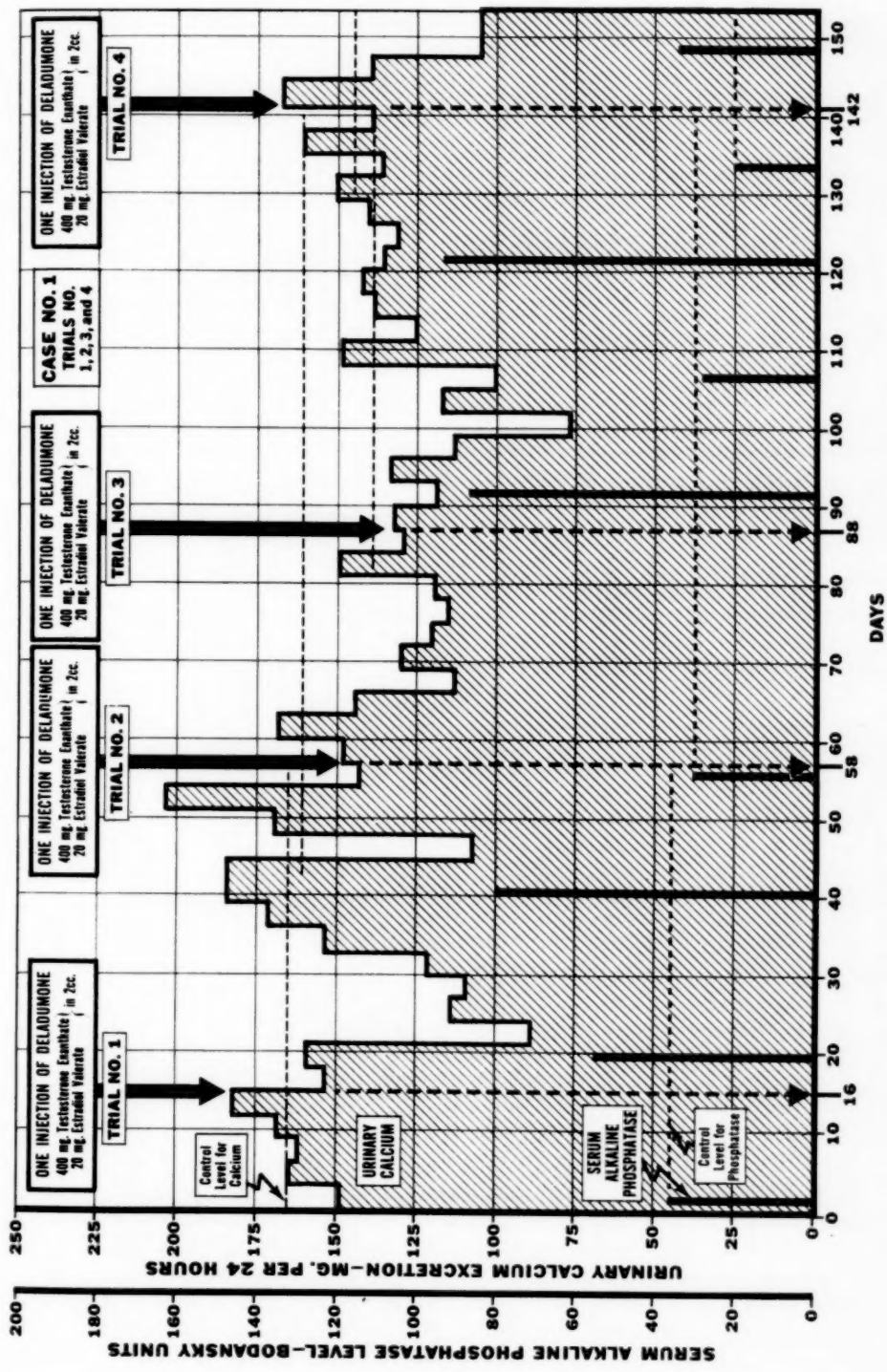

FIG. 1. Effect of Deladumone on urinary calcium excretion and the level of serum alkaline phosphatase in Paget's disease. (*Case 1*: V. V., female, aged 54.)

TABLE 2

Effect of Deladumone on Urinary Calcium Excretion and Serum Alkaline Phosphatase Level in Paget's Disease

(Case 2: J. S., male, aged 76)

Days	Urinary Calcium (mg./24 hrs.)	Serum Alk. Phosphatase (Bod. units)	Difference From Control Periods	
			Urinary calcium (mg./24 hrs.)	Serum alk. phosphatase (Bod. units)
No Treatment				
1–5	180	122	+28	0
4–6	127	125	−25	+4
7–9	150	—	−2	—
No Treatment (control periods for first injection)				
10–12	179	127	+27	+6
13–15	149	—	−3	—
16–18	132	115	−20	−6
19–21	126	—	−26	—
22–24	172	—	+20	—
Avge.	152	121		
*2 ml. Deladumone** (first injection)				
25–27	134	—	−18	—
28–30	88	128	−64	+7
31–33	65	—	−87	—
34–36	89	108	−63	−13
37–39	111	—	−41	—
40–42	126	—	−26	—
43–45	184	74	+32	−47
46–48	170	—	+18	—
49–51	148	80	−4	−41
52–54	150	—	−2	—
55–57	140	126	−12	+5
58–60	154	—	+2	—
No Treatment (control periods for second injection)				
46–48	170	—	+18	—
49–51	148	80	−4	−23
52–54	150	—	−2	—
55–57	140	126	−12	+23
58–60	154	—	+2	—
Avge.	152	103		
2 ml. Deladumone† (second injection)				
61–63	153	—	+1	—
64–66	102	—	−50	—
67–69	61	116	−91	+13
70–72	81	—	−71	—
73–75	80	110	−72	+7
76–78	117	—	−35	—
79–81	103	—	−49	—
82–84	105	—	−47	—
85–87	106	122	−46	+19
88–90	142	116	−10	+13
91–93	176	—	+24	—
94–96	153	—	+1	—
97–99	142	95	−10	−8
100–102	122	—	−30	—
103–105	126	99	−26	−4
106–108	—	—	—	—
109–111	167	—	+15	—
112–114	133	86	−19	−17
115–117	160	—	+8	—
118–120	139	38	−13	−65

* Regular Deladumone (R) containing 90 mg. of testosterone enanthate and 4 mg. of estradiol valerate per ml. of sesame oil.

† Special High Potency Deladumone (SHP) containing 200 mg. of testosterone enanthate and 10 mg. of estradiol valerate per ml. of sesame oil.

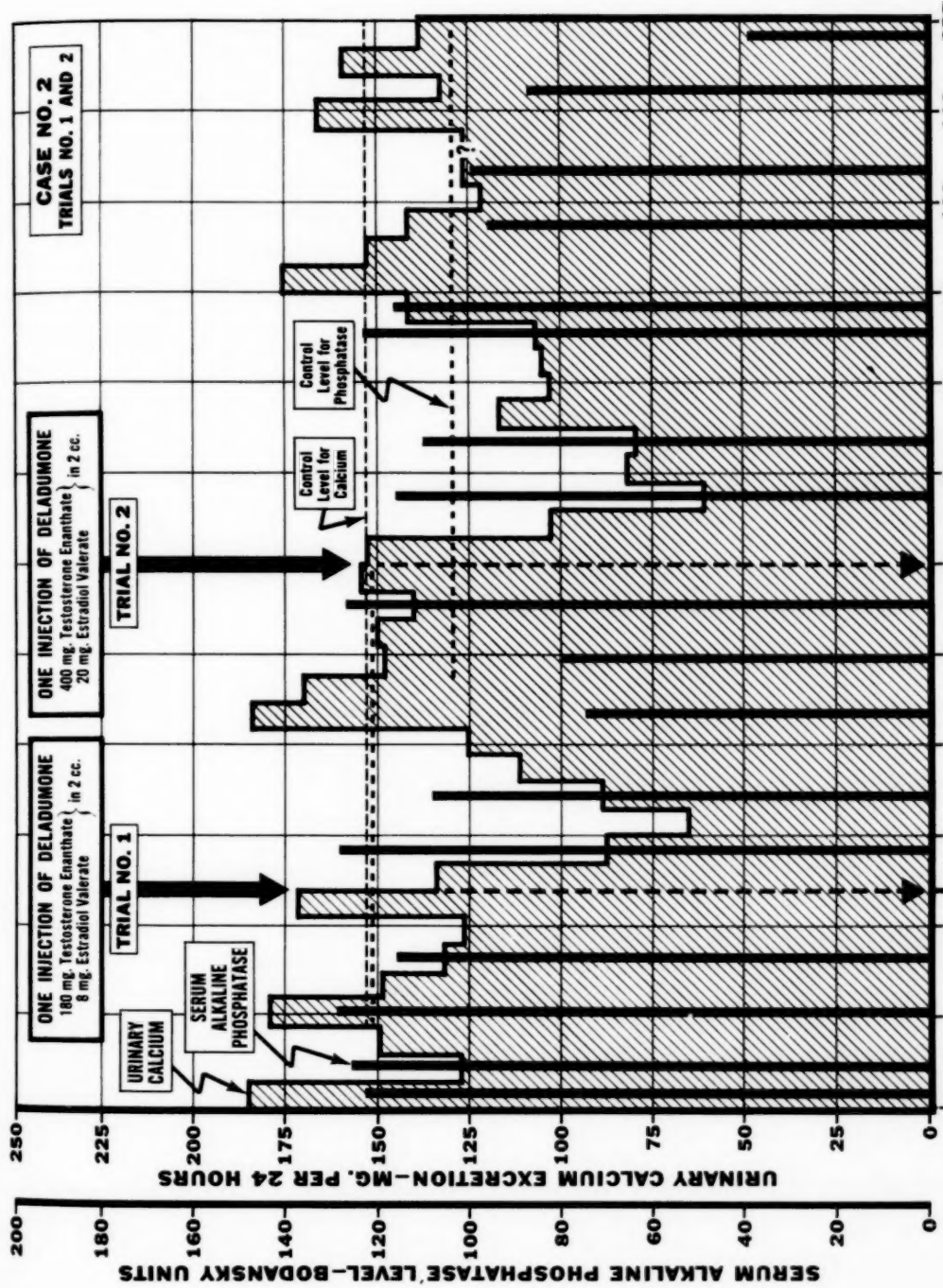
CASE NO. 2
TRIALS NO. 1 AND 2
ONE INJECTION OF DELADUMONE
180 mg. Testosterone Enanthate } in 2 cc.
8 mg. Estradiol Valerate
ONE INJECTION OF DELADUMONE
400 mg. Testosterone Enanthate } in 2 cc.
20 mg. Estradiol Valerate
TRIAL NO. 1
TRIAL NO. 2
URINARY CALCIUM
SERUM ALKALINE PHOSPHATASE
Control Level for Calcium
Control Level for Phosphatase
SERUM ALKALINE PHOSPHATASE LEVEL—BODANSKY UNITS
URINARY CALCIUM EXCRETION—MG. PER 24 HOURS
DAYS

FIG. 2. Effect of Deladumone on urinary calcium excretion and the level of serum alkaline phosphatase in Paget's disease. (*Case 2*: J. S., male, aged 76.)

and 180 mg. during the twenty-four days of preliminary observations, and averaged 152 mg. during the last fifteen days before therapy (Table 2 and Fig. 2). Following the injection of 2 ml. of Deladumone-R there was a marked decrease in the amount of calcium excreted in the urine. The fall was apparent within three to six days. The maximal 24-hour decrease of 87 mg. (57 per cent) below the average control value was reached nine days after the injection. Calcium excretion did not return to the pre-injection range until eighteen to twenty-one days after this injection. Subsequently there was a "rebound" increase in calcium excretion to a level above the average for the control period; this occurred on the twenty-first to twenty-seventh days after the injection. The same pattern of response was observed following the second injection, which consisted of 2 ml. of Deladumone-SHP. In this instance, the reduction in calcium excretion was apparent within three days after the injection. The maximal 24-hour decrease of 91 mg. (60 per cent) below the average control value was reached at nine days, and continued for twenty-four to twenty-seven days before excretion returned to the control range. Again a "rebound" increase in calcium excretion above the average control value was observed on the thirtieth to thirty-third days after the injection. As in the previous study, the minor fluctuations in the consecutive three-day values probably represented variations from exactly twenty-four hours in the timing of the urine collections.

Serum alkaline phosphatase level

In Case 1, determinations of the serum alkaline phosphatase level were carried out at irregular intervals (Table 1 and Fig. 1). The single measurement during the fifteen days of preliminary control observations yielded a value of 36 Bodansky units. The level of the enzyme rose above the control value (by as much as 100 per cent) immediately after the administration of Deladumone, and fell below the control value (by about 25 per cent) within twenty-one to forty-two days after the injection. The alkaline phosphatase measurements were performed with greater frequency and regularity in Case 2 (Table 2 and Fig. 2). The level fluctuated between 115 and 127 Bodansky units during the twenty-four days of preliminary observations, and averaged 121 Bodansky units during the last fifteen days before therapy. Again the enzyme level rose slightly above the control value shortly after the injection of Deladumone, and then fell below the control value (by about 30 per cent) within about twenty-one days after hormone administration.

Nitrogen balance

In Case 1, retention of nitrogen occurred from days 7 through 12 after the first injection of Deladumone-SHP, and from days 1 through 15 after the second injection of the same preparation. In Case 2, the nitrogen balance became more positive during days 4 through 6 following the injection of Deladumone-R, and during days 1 through 12 following the injection of Deladumone-SHP.

Other determinations

Urinary phosphorus excretion varied widely in both patients, and there appeared to be no consistent alterations associated with the administration of Deladumone.

Serum total calcium and inorganic phosphorus levels did not change significantly in either patient following the injections of Deladumone.

Roentgenograms

No recognizable alterations were observed in the involved areas of the skeleton during the relatively short courses of Deladumone therapy administered to these 2 patients.

RESULTS OF PREDNISONE THERAPY

An ancillary study was undertaken in 1 patient (Case 2) in order to determine the effects of corticosteroid medication on the urinary calcium excretion and the serum alkaline phosphatase level in Paget's disease, so that the results could be compared with those of Deladumone therapy. The data from this ancillary study are presented in Table 3 and Figure 3. Balance studies which were carried out in Case 2 immediately following the studies with Deladumone (Table 2 and Fig. 2). The data of the last 4 three-day periods of the Deladumone investigation serve as control values for the observations during corticosteroid therapy, which consisted of 30 mg. of prednisone by mouth daily for twenty-four days. Measurements were continued for one hundred and fifty-six days following the cessation of prednisone therapy. In presenting these data graphically it was necessary, because of this prolonged period of post-therapy observation, to employ a reduced time-scale as the abscissa for Figure 3; thus the abscissa in Figure 3 differs from that in Figures 1 and 2.

Urinary calcium excretion

In this study on Case 2, the 24-hour urinary calcium excretion varied between 133 and 167 mg., with an average of 150 mg., during the twelve days of preliminary control observations (Table 3 and Fig. 3). With the administration of prednisone there was a marked decrease in the amount of calcium excreted in the urine. The fall was apparent within the first three days. The maximal 24-hour decrease of 75 mg. (50 per cent) below the average control was reached nine to twelve days after the start of medication. The reduced urinary calcium excretion continued in the same range of approximately 91 mg. per twenty-four hours (about 40 per cent below the average pre-medication control value) throughout the twenty-four days of corticosteroid therapy.

After prednisone was stopped, calcium excretion continued at this decreased level for twenty-seven days. At this point, there was a further decrease to approximately 62 mg. per twenty-four hours (60 per cent below the average pre-medication control value and 20 per cent below the level during and im-

TABLE 3

Effect of Prednisone on Urinary Calcium Excretion and Serum Alkaline Phosphatase Level in Paget's Disease

(Case 2: J. S., male, aged 76)

Days	Urinary Calcium (mg./24 hrs.)	Serum Alk. Phosphatase (Bod. units)	Difference From Control Periods	
			Urinary calcium (mg./24 hrs.)	Serum alk. phosphatase (Bod. units)
No Treatment (control periods for prednisone)				
109–111	167	—	+17	—
112–114	133	86	−17	0
115–117	160	—	+10	—
118–120	139	38*	−11	*
Average	150	86		
Prednisone (30 mg./day)				
121–123	94	—	−56	—
124–126	90	113	−60	+27
127–129	116	—	−40	—
130–132	75	102	−75	+16
133–135	81	—	−69	—
136–138	91	—	−59	—
139–141	100	145	−50	+59
142–144	83	—	−67	—
No Treatment (control periods after prednisone)				
145–147	83	136	−67	+50
148–150†	96	—	−54	—
151–153	100	—	−50	—
154–156	85	50	−65	−36
157–159	78	—	−72	—
160–162	92	—	−58	—
163–165	83	—	−67	—
166–168	81	—	−69	—
169–171	79	—	−71	—
172–174	53	—	−97	—
175–177	60	74	−90	−12
178–180	68	—	−82	—
181–183	67	68	−83	−18
184–186	60	—	−90	—
187–189	75	68	−75	−18
190–192	117	—	−33	—
193–195	132	—	−18	—
196–198	136	91	−14	+5
199–201	175	—	+25	—
202–204	149	87	−1	+1
205–207	195	—	+45	—
208–210	210	87	+60	+1
211–213	208	—	+58	—
214–216	193	—	+43	—
217–219	181	80	+31	−6
220–222	160	—	+10	—
223–225	127	81	−23	−5
226–228	132	—	−18	—
229–231	122	93	−28	+7
232–234	110	—	−40	—
235–237	149	—	−1	—
238–240	135	87	−15	+1
241–243	137	—	−13	—
244–246	151	93	+1	+7
247–249	156	—	+6	—
250–252	156	101	+6	+15
253–255	123	—	−27	—
256–258	148	—	−2	—
259–261	110	88	−40	+2
262–264	168	—	+18	—
265–267	163	102	+13	+16
268–270	170	98	+20	+12
271–273	157	—	+7	—
274–276	184	—	+34	—
277–279	177	107	+27	+21
280–282	174	—	+24	—
283–285	153	93	+3	+7
286–288	195	—	+45	—
289–291	170	99	+20	+13
292–294	136	—	−14	—
295–297	175	113	+25	+27
298–300	154	—	+4	—

* Not included in average value.

† Fever for three days.

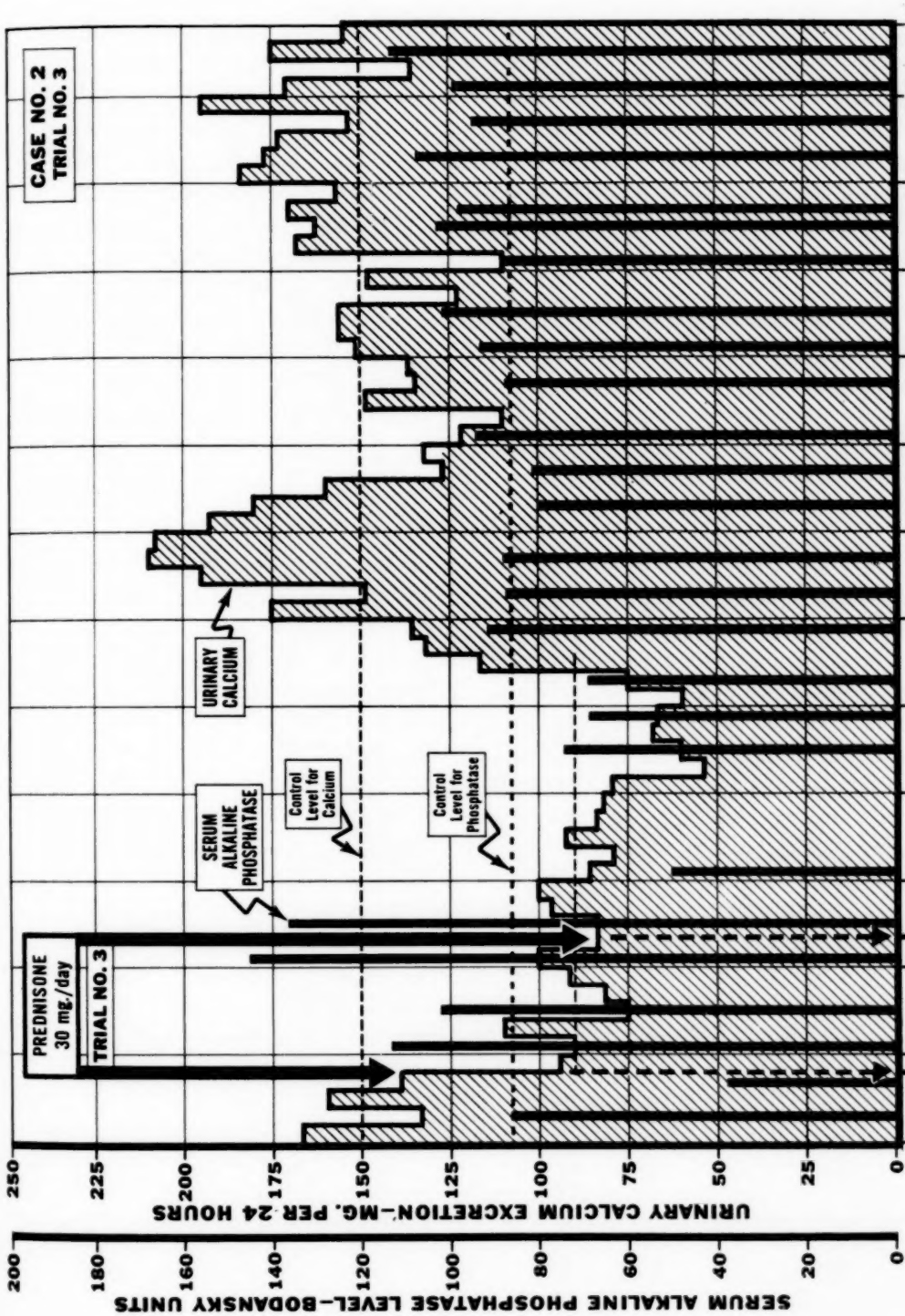

FIG. 3. Effect of prednisone on urinary calcium excretion and the level of serum alkaline phosphatase in Paget's disease. (*Case 2*: J. S., male, aged 76.)

mediately after discontinuing corticosteroid therapy). This further reduction in calcium excretion continued from the twenty-seventh to forty-second days after the termination of prednisone therapy. Following this, there was a marked "rebound" increase in calcium excretion from the forty-second to seventy-fifth days after the end of medication; this increase reached a maximal value of 210 mg. per twenty-four hours (40 per cent above the average pre-medication control value) on the sixtieth day. From the seventy-fifth to the eighty-fourth post-medication day there was a moderate decrease in the calcium excretion to a level below the control value, after which the excretion gradually rose, during the remaining sixty-six days of observation, to approximately 25 per cent above the average pre-medication control value. The urinary calcium excretion in Case 2 at the end of the corticosteroid phase of the investigation (Table 3) was slightly greater (about 16 mg. per twenty-four hours) than it had been approximately ten months previously at the start of the Deladumone phase (Table 2). As in the Deladumone phase of the study, the minor fluctuations in the consecutive three-day values probably represented variations in the exactness of the 24-hour urine collections.

Serum alkaline phosphatase level

In this study on Case 2, the serum alkaline phosphatase level during the twelve days of preliminary control observations (Table 3 and Fig. 3) was 86 Bodansky units, approximately 30 per cent below the level at the start of the Deladumone phase of the investigation four months previously (Table 2). The serum enzyme level rose significantly during prednisone therapy. The maximal increase of approximately 70 per cent was reached after twenty-one days of medication. Following discontinuation of prednisone, the serum alkaline phosphatase level fell to approximately 60 per cent of the control value in about nine days. During the twenty-seventh to forty-second days after the termination of the prednisone therapy, the phosphatase level rose to approximately 80 per cent of the pre-medication control values; and from the forty-second to seventy-fifth days of the post-medication period, the level fluctuated in approximately the control range. During the remaining seventy-two days of the study, the phosphatase level gradually rose to approximately 25 per cent above the pre-prednisone control value. The serum alkaline phosphatase level in Case 2 at the end of the corticosteroid phase of the investigation (Table 3) was within 10 per cent of the level observed approximately ten months previously, at the start of the Deladumone phase (Table 2).

ANALYSIS OF RESULTS

I. *Effects of Deladumone*

Sequence of events

Following the injection of Deladumone, there was an initial rise in the serum alkaline phosphatase level in association with a decrease in urinary calcium excretion (Table 4 and Fig. 4). These alterations persisted for two to five weeks

TABLE 4

Effect of Dosage of Deladumone on Urinary Calcium Excretion, Calcium Retention, and Serum Alkaline Phosphatase Level in Paget's Disease

Hormone preparation		Deladumone (R)*		Deladumone (SHP)†					
Dose		2 ml.		2 ml.					
How given		single injection once		single injection once					
When given		on Day 1		on Day 1					
Total amount of steroids:									
Testosterone enanthate		180 mg.		400 mg.					
Estradiol valerate		8 mg.		20 mg.					
Case No.		2		2		1		1 and 2	
Trial No.		1		2		1		Average—4 trials‡	
Control period (average):									
Length		15 days		15 days		15 days		15 days	
Urinary calcium		125 mg./24 hrs.		152 mg./24 hrs.		165 mg./24 hrs.		156 mg./24 hrs.	
Serum alk. phosphatase		121 Bod. units		103 Bod. units		36 Bod. units		53 Bod. units	
	Days After Injection	Difference From Control Values		Difference From Control Values		Difference From Control Values		Difference From Control Values	
		Urinary calcium (mg./24 hrs.)	Serum alk. phosphatase (Bod. units)	Urinary calcium (mg./24 hrs.)	Serum alk. phosphatase (Bod. units)	Urinary calcium (mg./24 hrs.)	Serum alk. phosphatase (Bod. units)	Urinary calcium (mg./24 hrs.)	Serum alk. phosphatase (Bod. units)
Single injection	1	—	—	—	—	—	—	—	—
	1–6	−41	+7	−25	—	−9	+18	−7	+16
	7–12	−75	−13	−81	+13	−63	—	−54	+13
	13–18	−33	—	−53	+7	−50	—	−46	+7
	19–24	+25	−47	−48	—	−3	+44	−32	+44
	25–30	−3	−41	−28	+16	+19	—	−11	+16
	31–36	−5	+5	+13	—	−27	—	−7	—
	37–42	—	—	−20	−8	+8	−6	−6	−7
	43–48	—	—	−26	−4	—	—	−26	−4
	49–54	—	—	−2	−17	—	—	−2	−17
	55–60	—	—	−3	−65	—	—	−3	−65
		Calcium Retained		Calcium Retained		Calcium Retained		Calcium Retained	
		total (mg.)	per day (mg.)	total (mg.)	per day (mg.)	total (mg.)	per day (mg.)	total (mg.)	per day (mg.)
Single injection	1	—	—	—	—	—	—	—	—
	1–12	696	58	633	53	435	36	369	31
	1–18	897	50	954	53	735	41	707	39
	1–21	801	38	1101	52	771	37	814	39
	1–24	747	31	1241	52	753	31	969	41
	1–30	765	25	1410	47	639	21	1121	37
	1–36	795	22	1332	37	801	22	1163	32
	1–42	—	—	1452	35	753	18	1199	29
	1–48	—	—	1608	33	—	—	1355	28
	1–54	—	—	1620	30	—	—	1367	25
	1–60	—	—	1638	27	—	—	1385	23

* Regular Deladumone (R) containing 90 mg. of testosterone enanthate and 4 mg. of estradiol valerate per ml. of sesame oil.

† Special High Potency Deladumone (SHP) containing 200 mg. of testosterone enanthate and 10 mg. of estradiol valerate per ml. of sesame oil.

‡ Case 1, Trial 1 (first injection); Case 1, Trial 2 (second injection); Case 1, Trial 4 (fourth injection); and Case 2, Trial 2 (second injection).

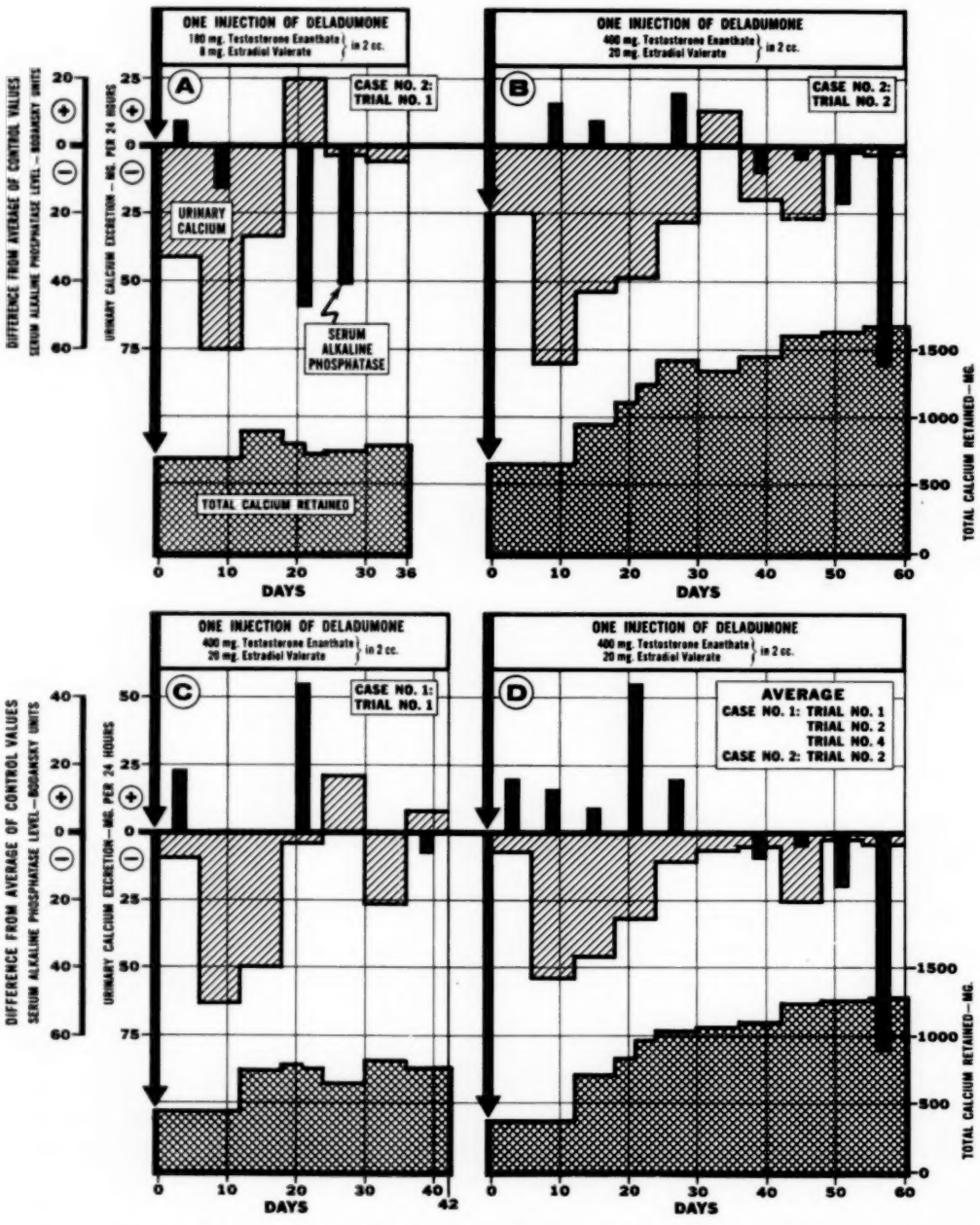

FIG. 4. Effect of dosage of Deladumone on urinary calcium excretion, calcium retention, and the level of serum alkaline phosphatase in Paget's disease.

(Table 5) after the injection, during which time there was retention of approximately 800 to 1400 mg. of calcium. Thereafter, calcium excretion returned to the pre-injection level (and in some instances showed a temporary "rebound increase" above this value) while the concentration of serum alkaline phosphatase declined to a level below the pre-injection value for four or more weeks

TABLE 5

Duration of Action of Deladumone and of Prednisone on Urinary Calcium Excretion and Serum Alkaline Phosphatase Level in Paget's Disease

Treatment	Total Dose of Hormone			Case No.	Trial No.	Duration of Action of Hormone Preparation	
	Testosterone enanthate (mg.)	Estradiol valerate (mg.)	Prednisone (mg.)			Duration of initial decrease in calcium excretion (days)	Duration of initial increase in serum alk. phosphatase level (days)
Deladumone							
Regular (2 ml.)	180	8	—	2	1	18 to 21 days	6 to 12 days
Special High Potency (2 ml.)	400	20	—	1	1	21 to 24 days	24 to 42 days
				1	2	24 to 27 days	—
				1	3	21 to 24 days	36 to 48 days
				1	4	over 12 days	over 6 days
				2	2	30 to 33 days	30 to 39 days
					Avge.	24 to 27 days	30 to 43 days
Prednisone (30 mg./day for 24 days)							
From start of medication	—	—	720	2	3	49 to 51 days	27 to 33 days
From end of medication	—	—	720	2	3	25 to 27 days	3 to 9 days

(Table 4 and Fig. 4). Because of the design of the study, it was not possible to determine which of these alterations was the first to be induced by Deladumone.

Effect of dosage

The effect of dosage can be observed by comparing in Case 2 the findings of Trial 1 with those of Trial 2. In Trial 1, the patient received an injection of 2 ml. of Deladumone-R which provided a total dose of 180 mg. of testosterone enanthate and 8 mg. of estradiol valerate, whereas in Trial 2, the patient received an injection of 2 ml. of the SHP Deladumone[1] which provided a total dose of 400 mg. of testosterone enanthate and 20 mg. of estradiol valerate (Table 4, and Figs. 2 and 4). The effect of the smaller dose on urinary calcium lasted for eighteen days; during this period there was retention of 897 mg. of calcium. The larger dose did not induce a significantly greater amount of calcium retention (954 mg.) during the first eighteen days after injection, but the duration of action was prolonged

[1] Approximately the same quantities of the two steroid esters present in 1 ml. of the Special High Potency Deladumone are available from E. R. Squibb & Sons in another preparation, Deladumone-2X. This contains 180 mg. of testosterone enanthate and 8 mg. of estradiol valerate per ml. of sesame oil. Therefore, a single injection of 2 ml. of Deladumone-2X would supply 360 mg. of the testosterone ester and 16 mg. of the estradiol ester. An even more concentrated preparation, Deladumone-4X, contains 360 mg. of testosterone enanthate and 16 mg. of estradiol valerate in each ml. of vehicle.

by approximately twelve days so that a greater amount of calcium (1410 mg.) was retained during the longer period of time.

Responsiveness of patients to Deladumone

The variation from patient to patient in the responsiveness to the same dose of Deladumone may be seen in a comparison of the findings of Trial 2 in Case 2 with those of Trial 1 in Case 1 (Table 4 and Figs. 2 and 4). In Case 2 the response to the larger dose of the hormone preparation was greater than in Case 1. This is indicated by the fact that in Case 2 (Trial 2) there was retention of 1410 mg. of calcium during a period of thirty days with an increase in the serum alkaline phosphatase level for a period of thirty to thirty-seven days, whereas in Case 1 (Trial 1) there was retention of only 771 mg. of calcium during a period of twenty-one days in spite of an increase in the serum alkaline phosphatase level for a period of twenty-seven to forty days. The response was greater in Case 2 even though the patient already had retained a considerable amount of calcium (897 mg.) following injection of the smaller dose of Deladumone (Trial 1). For this reason, a comparison of the response in Case 2 to the smaller dose of Deladumone (Trial 1) with the responses in Case 1 to the larger dose of Deladumone (Trials 1, 2 and 4) is without significance.

Duration of action of Deladumone

The duration of action of Deladumone can be determined from the durations of the initial decrease in the urinary calcium excretion and the initial increase in the serum alkaline phosphatase level (Table 5). Judging from the changes in urinary calcium, the duration of the action of a single injection of Deladumone was eighteen to twenty-one days with the smaller dose, and twenty-four to twenty-seven days with the larger dose. On the basis of the changes in serum alkaline phosphatase concentration, the duration of the action of a single injection of Deladumone was six to twelve days with the smaller dose, and thirty to forty-three days with the larger dose. The importance of employing several parameters and several dosage levels in evaluating the duration of action of a long-acting hormone preparation is apparent.

Sustained therapy

In Case 1, the third injection of the larger dose of Deladumone (Trial 3) was administered thirty days after the second injection of this same dose of Deladumone (Trial 2), at a time when the patient still was responding to the second injection with calcium retention. Trials 2 and 3 together represent sustained therapy in Case 1. When these two injections of Deladumone are considered together, the treatment induced calcium retention for seventy-eight consecutive days—the retention amounting to 2445 mg. As seen in Table 6 and Figure 5, the patient exhibited a greater response in Trial 3 than in Trial 2, both in the amount of calcium retained per day (41 mg. daily for thirty days versus 28 mg. daily for thirty days) and in the total amount retained per injection (1614 mg. in forty-eight days versus 831 mg. in thirty days). Thus, the

TABLE 6

Effect of Sustained (Repeated) Deladumone Therapy on Urinary Calcium Excretion, Calcium Retention, and Serum Alkaline Phosphatase Level in Paget's Disease

Hormone preparation	Deladumone (SHP)*
Dosage	2 ml.
How given	single injection repeated
When given	on Day 1 and Day 30
Total amount of steroids:	*per injection* / *both injections*
Testosterone enanthate	400 mg. / 800 mg.
Estradiol valerate	20 mg. / 40 mg.
Case No.	1
Trial No.	2, then 3
Control period (average):	
Length	15 days
Urinary calcium	161 mg./24 hrs.
Serum alk. phosphatase	30 Bod. units

	Days After First Injection	Days After Second Injection	Difference From Control Values		Per Period	
			Urinary calcium (mg./24 hrs.)	Serum alk. phosphatase (Bod. units)	Calcium Retained	
					total (mg.)	per day (mg.)
First injection	1	—	—	—	—	—
	1–6	—	−3	—	21	3
	7–12	—	−33	—	195	33
	13–18	—	−36	—	216	36
	19–24	—	−44	—	264	44
	25–30	—	−23	—	135	23
Second injection	30	1	—	—	—	—
	31–36	1–6	−36	+57	216	36
	37–42	7–12	−38	—	228	38
	43–48	13–18	−64	—	384	64
	49–54	19–24	−39	−2	237	39
	55–60	25–30	−29	—	177	29
	61–66	31–36	−19	+63	111	19
	67–72	37–42	−25	—	153	25
	73–78	43–48	−18	−10	108	18
	79–84	49–54	−11	—	69	11

	Days After First or Second Injection, Respectively	Cumulative, for First or Second Injection, Respectively		Days After First Injection	Cumulative, Both Injections	
		Calcium Retained			Calcium Retained	
		total (mg.)	per day (mg.)		total (mg.)	per day (mg.)
First injection	1	—	—	1	—	—
	1–12	216	18	1–12	216	18
	1–18	432	24	1–18	432	24
	1–21	570	27	1–21	570	27
	1–24	696	29	1–24	696	29
	1–30	831	28	1–30	831	28
Second injection	1	—	—	30	—	—
	1–12	444	37	1–42	1275	30
	1–18	828	46	1–48	1659	35
	1–21	1011	48	1–51	1842	36
	1–24	1065	44	1–54	1896	35
	1–30	1242	41	1–60	2073	35
	1–48	1614	34	1–78	2445	31
	1–54	1683	31	1–84	2514	30

* Special High Potency Deladumone containing 200 mg. of testosterone enanthate and 10 mg. of estradiol valerate per ml. of sesame oil.

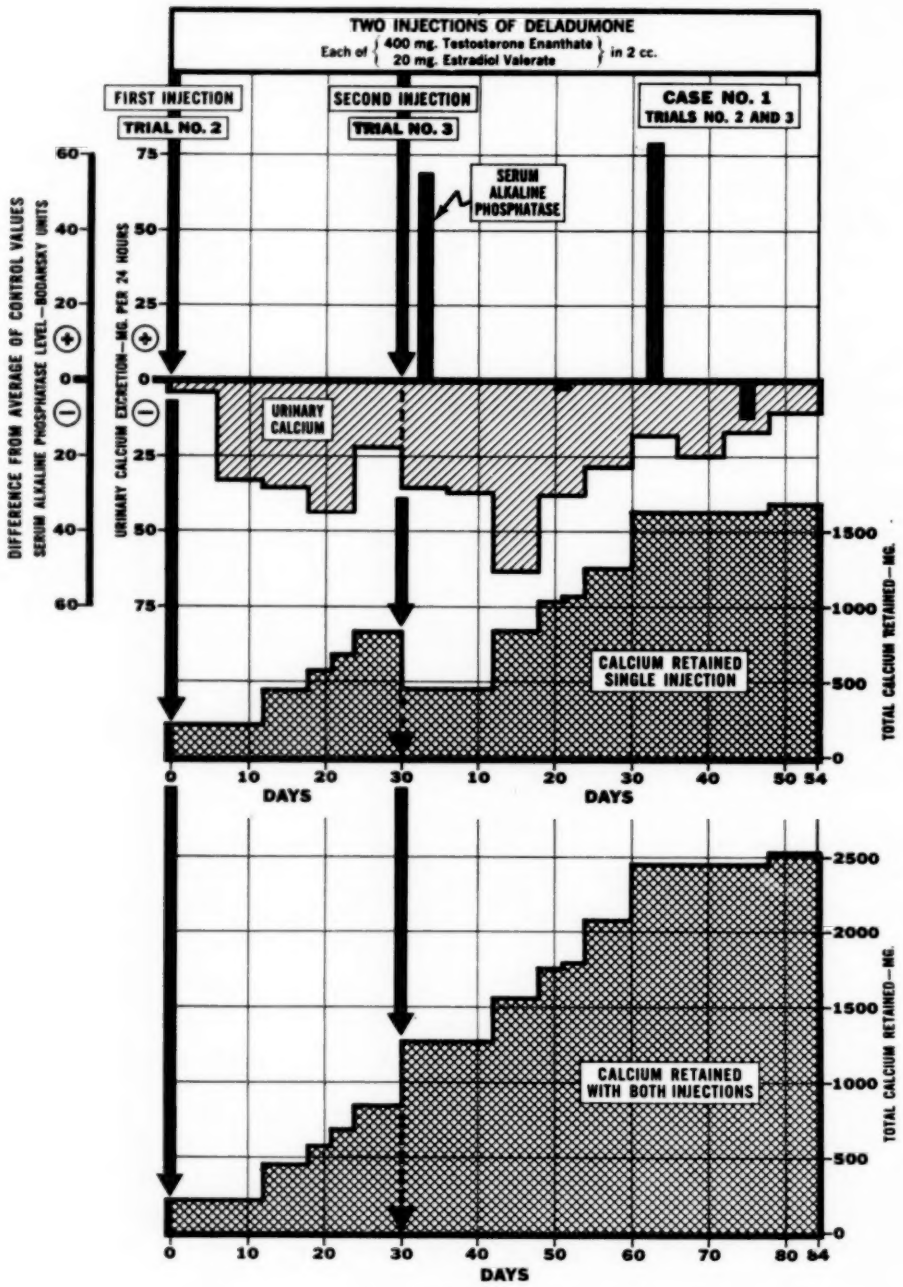

FIG. 5. Effect of sustained (repeated) Deladumone therapy on urinary calcium excretion, calcium retention, and the level of alkaline phosphatase in Paget's disease.

fact that following the injection of Deladumone in Trial 2 the patient was still responding with calcium retention at the time when another dose of the same amount of Deladumone was injected (Trial 3), led to a period of increased responsiveness, with even greater retention of calcium during Trial 3, though

831 mg. of calcium had already been retained during Trial 2. Furthermore, during the forty-two days preceding the injection of Deladumone in Trial 2, Case 1, there was a net retention of 753 mg. of calcium as a result of one injection of Deladumone (Trial 1) followed by a recovery period. Therefore, there is no indication that, with the amounts of Deladumone employed during the time periods in this study, the capacity of this patient to retain calcium under the influence of the hormone preparation was diminishing.

II. *Effects of Prednisone*

Sequence of events

During the administration of prednisone, there was an increase in the serum alkaline phosphatase level associated with a decrease in the urinary calcium excretion (Table 7 and Fig. 6). These changes persisted for the 24-day period during which the medication was given. Because of the design of the study, it was not possible to determine which of these alterations was the first to be induced by the prednisone. During the twenty-four days of medication, a total of 1428 mg. of calcium was retained. Following the cessation of prednisone therapy, urinary calcium excretion remained at a level below the pre-medication control value for a period of fifty-four days, during which time there was an additional retention of 3465 mg. of calcium. Thus, in a period of seventy-eight consecutive days beginning from the start of the twenty-four days of prednisone medication and ending fifty-four days after therapy had been discontinued, the patient retained a total of 4893 mg. of calcium. Thereafter, observations were continued for another seventy-eight days, during which urinary calcium excretion and the serum alkaline phosphatase level exhibited further alterations within or above the pre-medication range. During these last seventy-eight days the patient lost a total of 909 mg. of calcium. In the entire one hundred and eighty days from the start of prednisone medication, the patient retained 3984 mg. (net) of calcium; in the one hundred and fifty-six days following the cessation of prednisone medication, the patient retained 2556 mg. (net) of calcium.

The course of urinary calcium excretion and the serum alkaline phosphatase level following the cessation of the prednisone therapy will be considered in more detail. The alterations could be classified according to 7 distinct post-medication periods (Table 7, and Figs. 3 and 6), as follows:

Post-medication period I. In the first nine days after prednisone was discontinued, urinary calcium excretion remained at approximately the same level to which it had been reduced while the medication was being given. The serum alkaline phosphatase level remained elevated above the control value. During these nine days, the patient retained 513 mg. of calcium.

Post-medication period II. In the following eighteen days, urinary calcium excretion remained decreased at approximately the same level as during the period of medication. The concentration of serum alkaline phosphatase fell to a level distinctly below the pre-medication value. During these eighteen days, the patient retained 1206 mg. of calcium.

TABLE 7

Effect of Prednisone on Urinary Calcium Excretion, Calcium Retention, and Serum Alkaline Phosphatase Level in Paget's Disease

Hormone preparation	Prednisone
Dosage	30 mg. daily
How given	by mouth
When given	on Days 1 to 24
Total amount of prednisone	720 mg.
Case No.	2
Trial No.	3
Control period (average):	
Length	12 days
Urinary calcium	150 mg./24 hrs.
Serum alk. phosphatase	86 Bod. units

	Duration of Period (days)	Treatment	Days After Start of Medication	Days After End of Medication	Difference From Control Values		Total Calcium Retained				
					Urinary calcium (mg./24 hrs.)	Serum alk. phosphatase (Bod. units)	Per period (mg.)	Cumulative from start of medication		Cumulative from end of medication	
								days after start of medication	total (mg.)	days after end of medication	total (mg.)
Medication period	24	Started	1	—	—	—	—	1	—	—	—
		Continued	1-6	—	−58	+27	348	1-6	348	—	—
		Continued	7-12	—	−57	+16	345	1-12	693	—	—
		Continued	13-18	—	−64	—	384	1-18	1077	—	—
		Continued	19-24	—	−59	+59	351	1-24	1428	—	—
		Stopped	24	1	—	—	—	24	—	1	—
Post-medication period											
I	9	None	25-33	1-9	−57	+50	513	1-33	1941	1-9	513
II	18	None	34-51	10-27	−67	−36	1206	1-51	3147	1-27	1719
III	18	None	52-69	28-45	−86	−15	1551	1-69	4698	1-45	3270
IV	9	None	70-78	46-54	−22	+5	195	1-78	4893	1-54	3465
V	24	None	79-102	55-78	+34	−1	−813	1-102	4080	1-78	2652
VI	39	None	103-141	79-117	−15	+3	582	1-141	4662	1-117	3234
VII	39	None	142-180	118-156	+17	+16	−678	1-180	3984	1-156	2556

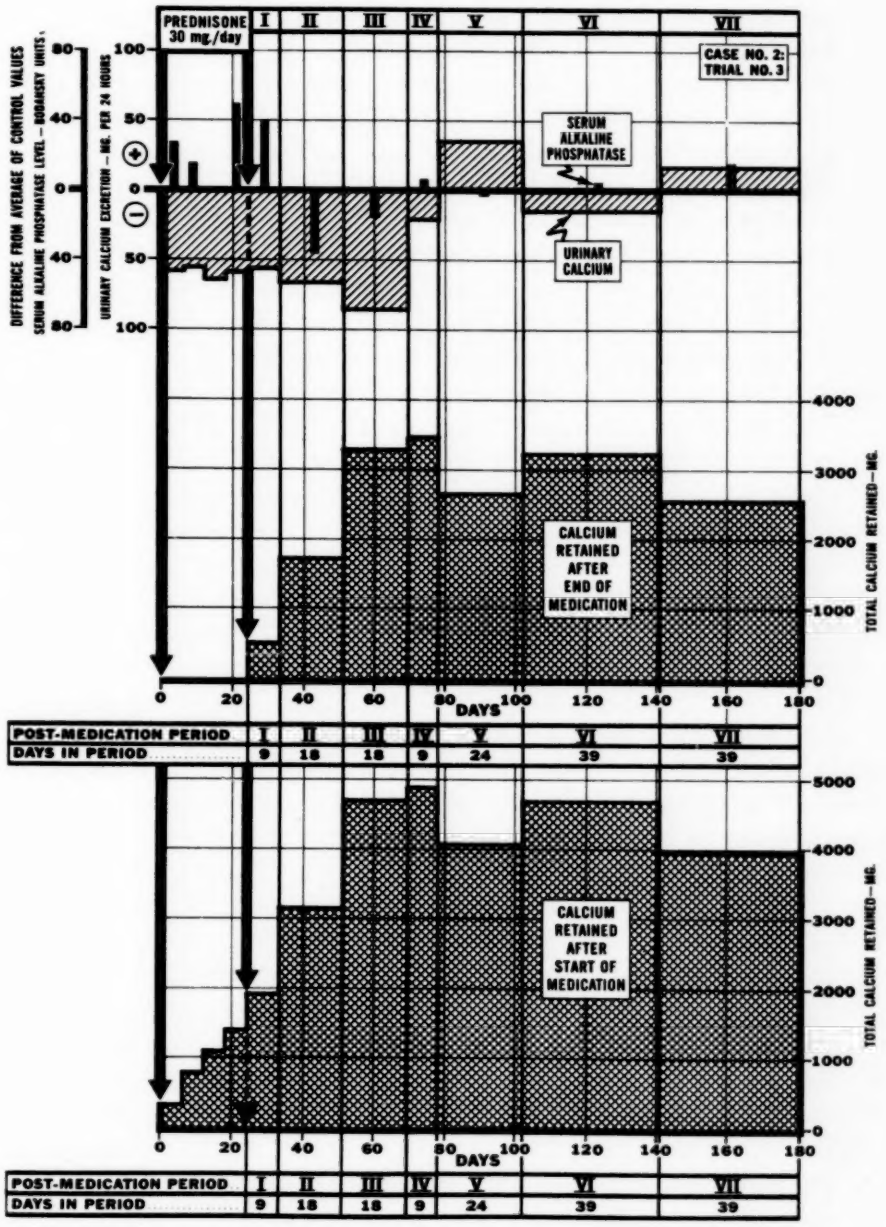

FIG. 6. Effect of prednisone on urinary calcium excretion, calcium retention, and the level of serum alkaline phosphatase in Paget's disease.

Post-medication period III. In the next eighteen days, urinary calcium excretion decreased further. Although the serum alkaline phosphatase level rose, it remained in a range moderately below the pre-medication values. During these eighteen days, the patient retained 1551 mg. of calcium.

Post-medication period IV. In the following nine days, urinary calcium excretion gradually returned to the pre-medication range and the serum alkaline

phosphatase level rose to the pre-prednisone control value. During these nine days, the patient retained 195 mg. of calcium.

Post-medication period V. In the next twenty-four days, a "rebound increase" phase occurred, during which urinary calcium excretion increased to a level considerably above the pre-medication value and the serum alkaline phosphatase concentration remained in the control range. During these twenty-four days, the patient lost 813 mg. of calcium.

Post-medication period VI. In the following thirty-nine days, urinary calcium excretion fell to slightly below the pre-medication value and the serum alkaline phosphatase level rose to slightly above the pre-treatment value. During these thirty-nine days, the patient retained 582 mg. of calcium.

Post-medication period VII. In the final thirty-nine days, urinary calcium excretion increased to a level considerably above the pre-prednisone value, and the concentration of serum alkaline phosphatase also rose to a level considerably above the pre-medication value. During these last thirty-nine days, the patient lost 678 mg. of calcium.

Duration of action of prednisone

The duration of action of prednisone can be determined from the duration of the initial decrease in urinary calcium excretion and from the duration of the initial increase in the serum alkaline phosphatase level following the cessation of the medication (Table 5). On the basis of the alterations in urinary calcium, the duration of action of prednisone after medication had been terminated was twenty-five to twenty-seven days. On the basis of changes in the serum alkaline phosphatase concentration, the duration of action of prednisone after the medication had been terminated was three to nine days. When the subsequent pronounced decrease in the serum alkaline phosphatase level was included as an index of the continuation of the corticosteroid activity, the duration of action of prednisone after the medication had been terminated appeared to be at least nine to twelve days. However, on Days 4 to 6 following the cessation of prednisone therapy, the patient had an attack of fever associated with a mild pneumonitis, lasting three days. This episode may have been associated with a marked increase in the production of corticosteroids by the adrenal cortex. If so, this temporary increase in endogenous corticosteroid activity may have moderately prolonged the metabolic alterations induced by the prednisone, and thus may have contributed to the unexpectedly long duration of action (nine to twenty-seven days) of prednisone after administration was discontinued.

III. *Comparison of Effects of Deladumone and Prednisone*

The data from these two studies make possible a comparison of the effects of Deladumone and prednisone on the indices of calcium and osseous metabolism in patients with advanced Paget's disease.

Sequence of events

Immediately after administration, both Deladumone and prednisone induced a rise in the serum alkaline phosphatase level and a decrease in urinary calcium

excretion. With Deladumone, the serum enzyme level usually remained elevated approximately as long as the urinary calcium excretion was decreased (about four weeks). In contrast, following the cessation of the prednisone medication, the serum alkaline phosphatase concentration fell promptly (in about one week) to a level considerably below the average pre-treatment control value while the urinary calcium excretion remained decreased, and the levels of both constituents remained below the pre-medication range for a considerable additional period of time (about seven weeks). Furthermore, the sequence of events was different for the two types of hormonal preparation after the patients ceased to exhibit calcium retention following the administration of the compounds. After administration of Deladumone, the serum alkaline phosphatase concentration fell to a level below the control value when the urinary calcium excretion rose to the pre-medication range or higher. In contrast, after ad-administration of prednisone, the serum alkaline phosphatase concentration rose to the control level or higher, when urinary calcium excretion rose to the control range or above. In addition, there were alterations in the measured metabolic indices during the post-medication periods following prednisone therapy which were not observed following the single injections of Deladumone.

Duration of action

Judging from the urinary calcium alterations, Deladumone given as a single injection has a duration of action apparently half that of prednisone given by mouth daily (about four weeks versus about eight weeks). However, judging from the serum alkaline phosphatase alterations, it appears that Deladumone as a single injection has a duration of action that is approximately five times greater than that of prednisone given by mouth daily (about five weeks versus about one week).

Amount of calcium retained

The total amount of calcium retained in a period of twenty-four days following a single injection of Deladumone was approximately two-thirds of that retained during the daily oral administration of prednisone for the same period of time (969 mg. versus 1428 mg.). Furthermore, because of the difference between the two types of hormonal preparation in the duration of effect upon urinary calcium excretion, the total amount of calcium retained following a single injection of Deladumone was less than one-quarter of that retained as a result of twenty-four days of prednisone therapy (1121 mg. versus 4893 mg.). However, when Deladumone was administered as sustained therapy by giving two injections separated by an interval of thirty days, the total amount of calcium retained during seventy-eight days was increased to half of that retained during a 78-day period as a result of twenty-four days of prednisone therapy (2445 mg. versus 4893 mg.). The net retention following sustained treatment with Deladumone, however, was closer to the net retention as a result of the prednisone therapy (2445 mg. versus 3984 mg.), owing to the fact that the losses of calcium were greater in the post-medication periods following prednisone than following Deladumone.

INTERPRETATION OF RESULTS

A comparison of the effects of Deladumone with those of prednisone on the indices of calcium and osseous metabolism measured in this study indicates that, in Paget's disease, these two types of hormonal preparation exert their influences on mineral and bone metabolism by different mechanisms. This is shown by the differences in the sequence of events, in the pattern and the duration of the alterations, and in the amount of calcium retained. The interpretation of the authors concerning these mechanisms follows. Contributory evidence will be considered subsequently in the Discussion.

Mechanism of action of Deladumone in Paget's disease

The most probable sequence of events in the action of Deladumone in Paget's disease is: 1) Deladumone stimulates osteoblastic activity, as indicated by an increase in the serum alkaline phosphatase level; 2) this results in increased bone formation with the utilization of increased amounts of calcium in the newly formed bone; 3) as a consequence of the incorporation of greater amounts of calcium in forming bone, the urinary calcium excretion falls; 4) as a result of the increased formation of calcified bone, the skeleton becomes stronger so that it is more resistant to the stresses and strains of weight-bearing; 5) as a result of the termination of the influence of Deladumone and of the decrease in physiologic stimulus that occurs when the bones become stronger, there is a temporary decrease in osteoblastic activity, as indicated by a decrease in the serum alkaline phosphatase level; 6) this results temporarily in decreased bone formation, which makes more calcium available for excretion in the urine; 7) the increased destruction of bone associated with Paget's disease continues, and this together with the decreased formation of bone, causes increased excretion of calcium in the urine; 8) as a result of the continued loss of calcium without sufficient compensatory bone formation, the skeleton becomes weaker, so that it is more responsive to the stresses and strains of weight-bearing; 9) as a consequence, osteoblastic activity is stimulated, as indicated by a rise in the serum alkaline phosphatase level; and 10) compensatory bone formation increases until it is commensurate with the degree of bone destruction involved in the Paget's disease process.

Mechanism of action of prednisone in Paget's disease

The most probable sequence of events in the action of prednisone in Paget's disease is: 1) prednisone in sufficient dosage (as in this study) inhibits the bone-destruction activity of the Paget's disease process;[2] 2) thus less calcium is re-

[2] The metabolic alterations observed in the current study during the administration of prednisone could be interpreted as indicating that prednisone had inhibited the renal mechanisms for excreting calcium in the urine and hence, by making more calcium available for bone formation, had increased the osteoblastic activity with a rise in the serum alkaline phosphatase level. Against this interpretation are two observations: 1) corticosteroid medication usually increases the urinary calcium excretion (5) instead of decreasing it; and 2) biopsies of bone from patients with Paget's disease treated with corticosteroids show inhibition of osteoblastic activity and of bone resorption (6).

moved from bone and consequently there is a decrease in urinary calcium excretion; 3) the decrease in calcium available for utilization in bone formation is reflected in decreased formation of calcified bone; 4) this results in a weaker skeleton which is more responsive to the stresses and strains of weight-bearing; 5) this in turn induces a compensatory increase in osteoblastic activity, as indicated by a rise in the serum alkaline phosphatase level; 6) because of the decreased availability of calcium, the osteoid matrix which is formed by the increased osteoblastic activity is not calcified (analogous to that observed in osteomalacia); 7) the continued influence of prednisone after approximately three to four weeks of administration results in an inhibition of osteoblastic activity, which is manifested by a marked decrease in the serum alkaline phosphatase level (if continued for a sufficient time, corticosteroid medication by this mechanism will lead to osteoporosis); 8) when prednisone therapy is discontinued, its inhibitory action on the Paget's disease process terminates and bone destruction again becomes excessive; 9) this results in more calcium being removed from bone and made available for bone formation; 10) at the same time, the termination of the inhibitory action of prednisone on osteoblastic activity is indicated by a rise in the serum alkaline phosphatase level above the prednisone-depressed range; 11) in the presence of an excess of uncalcified osteoid matrix and of increasing osteoblastic activity, a large proportion of the calcium being released from bone is utilized for the calcification of pre-formed matrix and for the formation of additional calcified bone; 12) this is manifested by a further decrease in urinary calcium excretion;[3] 13) as a result of the increased formation of calcified new bone, the skeleton becomes stronger so that it is more resistant to the stresses and strains of weight-bearing; 14) in association with the decrease in the physiologic stimulus which occurs when the bones become stronger, the osteoblastic activity does not increase rapidly to the pre-prednisone level, as reflected by a serum alkaline phosphatase level which remains below the pre-medication level; 15) as a result, less calcium is used for

[3] The utilization of a greater amount of calcium for bone formation may be a consequence also of a temporary decrease in the endogenous influences which function physiologically to inhibit bone formation, namely, the endogenous corticosteroids. The production of these steroids by the adrenal cortex may be decreased by a temporary inhibition of the adrenal gland induced by the administration of prednisone.

There is another possible explanation for the further decrease in the urinary calcium excretion in Post-medication Period III. On Days 4 to 6 following the cessation of the prednisone therapy, the patient had fever associated with a mild pneumonitis. This episode lasted three days, and might have been associated with a marked increase in endogenous corticosteroid production which could have induced a pronounced inhibition of the bone-destructive process of the Paget's disease; this would be characterized by a considerable decrease in urinary calcium excretion and by a rise in the serum alkaline phosphatase level such as was observed in Post-medication Period III. Against this interpretation is the point that the patient did not exhibit the alterations in the pattern of urinary calcium excretion and of the serum alkaline phosphatase level until twenty-one days after the episode of fever. However, a temporary increase in endogenous corticosteroid production may have moderately prolonged the metabolic alterations induced by the prednisone, and thus may have contributed to the unexpectedly long duration of action (nine to twenty-seven days) of the corticosteroid medication following its termination.

bone formation and urinary calcium excretion rises; 16) the increased bone destruction of the Paget's disease process escapes completely from corticosteroid inhibition, and temporarily becomes greater than before the medication was given; consequently, there is a marked increase in the excretion of calcium in the urine; 17) as a result of the continued loss of calcium from bone without compensatory bone formation, the skeleton becomes weaker so that it is more responsive to the stresses and strains of weight-bearing; 18) thus osteoblastic activity is stimulated, as indicated by a rise in the serum alkaline phosphatase level; and 19) compensatory bone formation increases until it is commensurate with the degree of bone-destructive activity of the Paget's disease process.

DISCUSSION

I. *Effect of Anabolic Steroids in Paget's Disease*

Previous studies

Anabolic steroids (androgenic and estrogenic hormones of gonadal and adrenocortical origin) stimulate the growth of protein and osseous tissues (7). In Paget's disease, the localized bone destruction creates a need for increased (compensatory) bone formation to improve the weight-bearing capacity of the weakened skeleton. Furthermore, many patients with this osseous disorder have been subjected for a prolonged period to a less-than-optimal rate of bone formation because of the reduction in physical activity which results when weight-bearing is accompanied by bone pain. On the basis of these considerations, Albright and one of us (ECR) in 1948 suggested a trial of estrogenic hormone therapy in patients with Paget's disease (8). However, the use of estrogen alone is considered by many physicians to be undesirable in males because of the possibility of inducing the unwanted effects of breast enlargement and tenderness, and suppression of testicular function. For this reason, Gordan studied the effect of therapy with androgen alone in men and women with Paget's disease, and in 1951 he reported (9) that this type of anabolic steroid therapy induced a decrease in bone pain and a reduction in hypercalciuria similar to that reported by one of us (ECR) (10) in patients with postmenopausal and senile osteoporosis. In spite of these encouraging results, however, many physicians are reluctant to employ anabolic steroid therapy with androgen alone in females because of the possibility of inducing undesirable manifestations of masculinization.

The studies on osteoporosis (10) indicated that anabolic therapy with androgen combined with estrogen was superior to therapy with either androgen or estrogen alone in inducing bone formation, as indicated by the retention of calcium and of phosphorus in the proportion of these constituents in adult healthy bone. The development of a long-acting injectable hormone preparation (Deladumone), in which an androgenic component (testosterone enanthate) is combined with an estrogenic component (estradiol valerate) in a ratio that reduces to a minimum each unwanted single-hormone effect (masculinization or feminization), provided a practical agent with which to evaluate the beneficial effects of anabolic steroid therapy in both men and women with Paget's disease. The hazard of inducing

undesirable manifestations involving the genital organs or the accessory sexual structures is minimal. Kolb (11) in 1959 reported the results of prolonged treatment of Paget's disease over a period of more than four years with testosterone enanthate (Delatestryl, Squibb) in 2 cases and with Deladumone in 2 cases. He reported that these compounds, in a dosage of 1 to 3 ml. intramuscularly as a single injection once every three weeks, were effective in relieving bone pain and reducing hypercalciuria. Roentgenograms showed increased density of the bones after one to two years of continuous therapy. Undesirable manifestations were minimal; there was no edema. In one patient, there was suggestive evidence that Deladumone was more effective than Delatestryl in reducing hypercalciuria. As a result of his experiences with these 2 hormone preparations during a period of more than four years, Kolb was impressed by their effectiveness, potency, and freedom from undesirable effects.

The present studies

The studies reported here confirm and extend the observations of Kolb (11) on the effectiveness of Deladumone in Paget's disease. Pain, when present, was relieved and the excessive excretion of calcium in the urine was decreased to within the physiologic range. The metabolic studies showed that when a sufficiently large dose of this androgen-estrogen combination is administered as a single injection (such as 4 ml. of Deladumone Regular[4] containing 360 mg. of testosterone enanthate and 16 mg. of estradiol valerate), it induces calcium retention for at least thirty days. Furthermore, when a dose of this magnitude is repeated every thirty days, a sustained response is achieved and subsequent doses induce greater retention than does the first injection of the series. Apparently large doses of Deladumone are more effective than smaller amounts in inducing calcium retention in Paget's disease, and when the larger dose is injected about once very four weeks there is no evidence for at least five months of a decrease in the capacity of the patient to retain calcium under these circumstances. The metabolic studies also indicate that although there is a tendency toward a slight "rebound increase" in urinary calcium excretion after the effect of an injection of Deladumone has disappeared, the amount of calcium lost in this manner is far less than the amount retained, so that there is a sizable net retention of the mineral; nevertheless, all patients are not equally responsive in terms of calcium retention to a given dose of the hormone preparation. In these studies, the injections of Deladumone were well tolerated, and induced no unwanted manifestations (such as masculinization or feminization). The data support the interpretation that this hormone combination increases osteogenesis in patients with Paget's disease and during the period of treatment improves the weight-bearing capacity of the skeleton. The effectiveness of Deladumone in relieving bone pain in a variety of osseous disorders has been observed by other investigators (12). In the present studies, its anabolic effect

[4] Deladumone 2-X contains twice these amounts, and Deladumone 4-X contains four times these amounts.

on protein tissues was demonstrated by the retention of nitrogen in both patients, and by the gain in weight in one of them during therapy.

II. *Effect of Anti-anabolic (Corticoid) Steroids in Paget's Disease*

Previous studies

The stimulating effect of anabolic steroids on the growth of protein and osseous tissues is in direct contrast to the inhibiting effect of anti-anabolic steroids (glucocorticoid hormones of adrenocortical origin, such as hydrocortisone) on the growth of these tissues (7). Consequently, the demonstration in 1955 by Albright and Henneman (6) that large doses of adrenocorticotropic hormone (ACTH) or of cortisone would induce an immediate fall in urinary calcium excretion in patients with Paget's disease was a paradoxical finding. Their observations, however, were consistent with earlier reports of other investigators. In 1932 and 1936 Berman (13) reported that adrenocortical extract administered continuously for a period of two years induced marked clinical improvement and a progressive decrease in the elevated serum alkaline phosphatase level in patients with Paget's disease. Kay and associates (14) reported in 1934 that adrenocortical extract relieved bone pain in this disorder. In 1952 Falk (15) treated a case of Paget's disease with cortisone and observed a similar beneficial response.

In the metabolic balance studies of Albright and Henneman (6) the usual dosage was 600 mg. per day for cortisone, 60 mg. per day for hydrocortisone, and 20 to 30 mg. per day for prednisone. Their investigations revealed that, with corticosteroid therapy, there was an immediate fall in the elevated urinary calcium excretion, a disappearance of osteoclasts from bone (biopsy specimens), and at times a moderate increase in the serum alkaline phosphatase level. These alterations were interpreted as corticosteroid suppression of the primary localized bone-destruction process of Paget's disease, in association with a decrease in the amount of calcium released from bone, resulting in less calcium available for excretion in the urine and for utilization in the accelerated compensatory bone repair, and thus a temporary increase in osteoblastic activity (as in the body-fluid calcium deficiency of osteomalacia). However, as the corticosteroid medication was continued, there was a secondary rise in urinary calcium excretion after approximately fifteen to twenty-one days of therapy associated with disappearance of the osteoblasts from bone (biopsy specimens), and a decrease in the elevated serum alkaline phosphatase values to below the control levels. These findings were interpreted as corticosteroid suppression of osteoblastic activity in association with a decrease in bone formation (which, if continued, would lead to osteoporosis similar to that observed in Cushing's syndrome). A fall in the elevated serum alkaline phosphatase level of patients with Paget's disease during ACTH therapy has been reported by others (16, 17). Albright and Henneman (6) observed that when corticosteroid therapy was discontinued, there was again a fall in urinary calcium excretion. This was interpreted as an increase in bone formation when the inhibiting effect of the corticosteroids on

osteoblastic activity was eliminated and compensatory bone formation resumed. These investigators also reported that, in patients with severe Paget's disease, corticosteroid therapy may produce a striking decrease in the augmented cardiac output and mild to marked clinical improvement. Subsequently, Albright, Henneman and their associates [Rapaport *et al.* (18)] published a more detailed report on the alterations in cardiac output induced by corticoid therapy in Paget's disease.

The present studies

Our studies confirm and extend the observations of Albright and Henneman (6) on the suppressing effect of corticosteroid therapy in Paget's disease. The administration of 30 mg. of prednisone induced a prompt fall in urinary calcium excretion accompanied at first by a rise in the serum alkaline phosphatase level. This is interpreted as indicating that prednisone inhibited the excessive localized bone-destruction process of Paget's disease, and thus reduced the amount of available calcium for excretion in the urine and for utilization in the formation of calcified bone. During this phase (in which the body fluids were similar to those in osteomalacia because of insufficient mobilization of calcium) osteoblastic activity was increased, just as it is in osteomalacia arising from insufficient absorption or excessive excretion of calcium. The mechanisms involved in the production of osteomalacia are discussed in detail elsewhere by one of us (ECR) (19). This phase of the response to prednisone in the studies on Paget's disease reported here lasted approximately thirty days (through both the administration period and Post-medication Period I). At this point, corticosteroid inhibition of the excessive localized bone-destruction process of Paget's disease continued, and inhibition of osteoblastic activity commenced, as indicated by a marked fall in the serum alkaline phosphatase level (Post-medication Period II). Since prednisone had been discontinued after twenty-four days of administration, its inhibiting effect on osteoblastic activity was of short duration and lasted for less than eighteen days (through Post-medication Period II). This was followed by resumption of compensatory bone formation (Post-medication Period III) in association with utilization of greater amounts of calcium than before corticosteroid inhibition of the osteoblasts because of the uncalcified osteomalacic matrix which had been produced. It appears that the inhibitory effect of corticosteroid therapy on the Paget's bone-destruction process terminated also at about the same time as the resumption of increased compensatory bone formation (at the start of Post-medication Period III). However, because of increased utilization of calcium to calcify the already formed osteoid matrix the remaining amount of calcium available for excretion in the urine was less than before, and therefore urinary calcium excretion was decreased still further (Post-medication Period III) than it had been under the inhibition of excessive bone destruction. The phase of increased utilization of calcium for bone formation persisted for at least eighteen days (through Post-medication Period III) and then became masked by the accelerated activity of the localized bone destruction process of the Paget's disease as it escaped from the corticoid-

induced inhibition (Post-medication Periods IV and V). In about thirty days (by the end of Post-medication Period V), the rates of bone formation and bone resorption began to return toward a state of dynamic equilibrium (Post-medication Period VI). Finally, one hundred and seventeen days after the termination of prednisone medication, the patient reached a phase (Post-medication Period VII) in which both the pathologic bone-destruction process and the physiologic compensatory bone-formation process were gradually increasing, the rate of the former being definitely greater than that of the latter.

The data from the present studies support the concept that the physiologic activities of the osteoblasts concerned with compensatory bone formation are more resistant to the inhibitory action of corticosteroid therapy than the pathologic activities of the unknown elements involved in the characteristic localized bone resorption of Paget's disease. The apparently prolonged effect (twenty-five to twenty-seven days) of prednisone after administration may have been related to the episode of fever associated with a mild pneumonitis on days 4 to 6 following the cessation of the prednisone therapy, since increased corticosteroid production by the adrenal cortex may have prolonged the metabolic alterations. Thus it appears that corticosteroid medication inhibits the pathologic localized excessive bone destruction of Paget's disease, and thereby at first creates changes in the body fluids similar to those seen in osteomalacia, in association with increased osteoblastic activity; subsequently, as medication is continued, it inhibits the osteoblastic activity and thus secondarily creates an osseous state which, if continued, could lead to osteoporosis.

III. *Effect of Anabolic and Anti-anabolic Steroids in Combination, in Paget's Disease*

The evidence reviewed in this communication indicates that prolonged administration of corticosteroids in patients with Paget's disease may not only have the beneficial effect of inhibiting the pathologic process of bone destruction while the medication is being administered, but may also have the undesirable effects of inducing osteoporosis during therapy and of accelerating the process of bone destruction when the medication is discontinued. Extensive data supporting the contention that anabolic steroid therapy will prevent the development of osteoporosis during medication with corticoid substances have been reviewed elsewhere by one of us (ECR) (7). This preventive action of anabolic steroid therapy is one important reason for administering Deladumone simultaneously with corticosteroids in the treatment of Paget's disease, as in the treatment of other conditions in which corticosteroids are given for prolonged periods.

In addition, the present data favor the interpretation that Deladumone and corticosteroid therapy induce their favorable effects in Paget's disease by different mechanisms, as indicated by the differences in the sequence of events, in the pattern and duration of the alterations, and in the amount of calcium retained. The authors believe that Deladumone stimulates bone formation and that corticosteroid medication inhibits bone destruction and also the mineral

phase and then the protein phase of bone formation. This leads to the obvious suggestion that in order to obtain a greater favorable response involving the beneficial effects of both types of steroids, these compounds should be administered simultaneously. Thus the effect of an androgen-estrogen preparation (Deladumone) combined with a corticosteroid preparation such as triamcinolone (Kenacort, Squibb) should be evaluated in patients with severe Paget's disease. Evidence already exists that the anabolic androgen-estrogen preparation will prevent corticoid-induced osteoporosis; it remains to be determined whether accelerated bone destruction will occur under these circumstances when both medications are terminated. It seems probable that a greater net calcium retention could be achieved by combining anabolic and anti-anabolic steroids in the treatment of Paget's disease. A greater net calcium retention would improve the weight-bearing capacity of the weakened skeleton to a greater degree than appears possible with either type of steroid medication alone. The proposal to combine both types of steroid therapy in Paget's disease has been advanced also by Kolb (11). Such studies now are in progress.

SUMMARY

Two cases of advanced Paget's disease (osteitis deformans) with hypercalciuria and a markedly elevated level of serum alkaline phosphatase were studied in order to evaluate the influence on the clinical and the metabolic aspects of parenteral anabolic steroid therapy. The preparation used was Deladumone, a combination of the long-acting steroid esters, testosterone enanthate and estradiol valerate; the proportions are balanced so that undesirable single-hormone effects (either androgenic or estrogenic) are minimized. Metabolic balance studies were performed on these 2 patients for one hundred and fifty-three and three hundred consecutive days, respectively, during which Deladumone (at two dosage levels) was administered as a single injection on 6 separate occasions.

When a sufficiently large dose of the androgen-estrogen preparation was administered as a single injection (*e.g.*, 4 ml. of Deladumone Regular containing 360 mg. of testosterone enanthate and 16 mg. of estradiol valerate), bone pain was relieved, nitrogen was retained, weight was gained, and the excessive excretion of calcium in the urine was decreased to the physiologic range for at least thirty days. When a dose of this magnitude was repeated every thirty days, sustained calcium retention was achieved. Such doses appeared to be more effective than smaller amounts in the treatment of Paget's disease. The injections were well tolerated by the patients, and induced no undesirable manifestations such as masculinization or feminization.

The data support the interpretation that this androgen-estrogen preparation (Deladumone) increases osteogenesis in patients with Paget's disease and during the period of treatment improves the weight-bearing capacity of the weakened skeleton. The results of ancillary studies indicate that the hypercalciuria of Paget's disease can be eliminated by corticosteroid (prednisone) therapy, and that the favorable effects of these steroids are produced by a mechanism different from that of the anabolic steroids. Corticosteroids act by inhibiting the localized

process of excessive bone destruction, in association with inhibition of the mineral phase and then the protein phase of bone formation. Thus, in advanced Paget's disease, it may be possible to achieve an enhanced favorable response and a more pronounced improvement in the weight-bearing capacity of the weakened skeleton by the administration of a corticosteroid and an anabolic androgen-estrogen preparation simultaneously.

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ULTRA-CAUTIOUS LIVING: A POTENTIAL HAZARD FOR THE PATIENT WITH CHRONIC DISEASE

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In a comparative study of antemortem diagnosis and the pathologic findings at autopsy, Monroe (1) reported that a number of older patients who were thought to have had pulmonary emphysema showed no trace of respiratory disease; their clinical history of shortness of breath on exertion was therefore explained on the basis of physical unfitness, the end-result of devotion to regimens of inactivity. Unfortunately, the adage, "Conserve the energies of older people," has been so frequently employed as to have acquired the prestige of a validated legend. However, it has become clear that the muscular atrophy which follows programs of excessive rest leads ultimately to invalidism, with progressive functional impairment of the respiratory and cardiac systems.

Physical exercise. Marvin (2) states that, "During the past several years a number of heart specialists apparently have become convinced that regular physical exercise may be beneficial in retarding or preventing the development of coronary atherosclerosis." He quotes Paul White as saying that "Work has a beneficial effect on body, mind, and soul in any occupation in which it is possible for the cardiac patient to engage. Idleness breeds unhappiness and is actually bad for the health." He also quotes Howard Rusk as emphasizing the value of stress in a dynamic, useful life: "We learned, in the middle of World War II, all of the deconditioning phenomena that come from just putting a person to bed: negative calcium balance, loss of vitamins, deconditioning of the myocardium—all of the things that we now accept as the sound reason for early ambulation after disease or surgery."

Adrenal stimulation. The physiologic advantages of physical exercise will naturally follow the pursuit of enterprising excursions into the outside world, including activities devoted to play as well as work. The prescription of ultracautious living has often been given to people who suffer from chronic respiratory disease, in whom shortness of breath would appear to offer sufficient justification for a rest program. However, patients with bronchial asthma and pulmonary emphysema are benefited by adrenaline and cortisone—hormones from the medulla and cortex of the adrenal gland, both of which tend to create a sensation of heightened awareness, excitement and trepidation. For men to experience alarm was said by Selye (3) to be an advantage in maintaining the function of the adrenal glands. Cannon showed years ago that emotional excitation stimulates an outpouring of secretions from the adrenal. Recent experimental studies by Richter (4) have revealed that when wild rats are kept in cages for several months and are well fed and protected, severe adrenal atrophy takes

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place. Clinicians have also observed that patients with bronchial asthma, when suddenly exposed to an exciting situation, such as a fire in the house, may abruptly become free of wheezing. In an experience of this kind, it is assumed that some pharmacologic substance from the adrenal gland has entered the circulation.

Adventure is man's way of heightening the awareness of existence. "Oft have I surmised and finally have I learned that peril is the chiefest way to happiness," said Christopher Marlowe. A life which includes some hazard seems to be a requisite for many mature men and women who utilize their capacity for individual inquiry, exploration, independent thinking and action. This challenging philosophy is naturally opposed by those who are more pastoral by nature or those who believe in the eventual rewards of contemplation and renunciation.

Anxiety and tension. So much prestige has been allotted in contemporary culture to various forms of sublimation, that inhibition of man's natural inclinations has gained ardent disciples. Gospels of ultra-cautious living are often adopted by men whose individual bias does not permit them to recognize the consequences of personal deprivation, such as anxiety, tension and depression. "Boredom tires a woman but ruins a man," says the Chinese proverb. Expression of the craving for excitement has been acknowledged as a necessity for children, for otherwise they scream; but it should be emphasized that a similar necessity exists for many adult men and women. For the individual to fulfill his legitimate natural inclinations was considered by Samuel Butler a higher aim than to husband unspent moments by withdrawing into an illusory safe enclosure. An apparently peaceful life may breed tension and anxiety.

Hyperventilation. Clinical experience has shown that states of anxiety are frequently accompanied by over-breathing, *i.e.*, breathing in excess of the body's needs for oxygen. This so-called hyperventilation lowers the carbon dioxide content of the blood in some cases to such an extent as to produce bronchospasm, laryngospasm, and spasm of the coronary arteries. Symptoms of nervousness, dizziness, weakness, and the muscle spasm of tetany have been noted as consequences of breathing more air than is needed to satisfy one's energy requirement.

On the other hand, when pulmonary ventilation is increased by natural activities, such as physical exercise, the carbon dioxide produced performs the valuable function of preventing undue constriction of the bronchi, and the cerebral and coronary arteries.

Cautious living. Although it is generally difficult, if not impossible, to make any radical change in another person's accustomed attitude of mind, the physician may exert some influence in encouraging a fuller life for his patient if his own personal bias veers in that direction. If the doctor himself strives to live a warm human life, in addition to striving for expert knowledge, he may countenance an adventurous outlook. Otherwise, he may counsel a program of cautious living. Whether life will be prolonged thereby or not, it will certainly seem longer to those who have endured an existence of excessive austerity.

An example of misguided self-interest is seen in Chekhov's story, "A Woman

of Intrigue." A beautiful woman talks to a famous novelist whom she met on a train in Moscow. She said that she did not marry the man she loved, but instead chose a rich old man. In that way her mother and sister were well provided for. Some years later when her husband suddenly died she was free to marry the man she loved, because he still loved her. When asked why she then did not marry him, the woman replied: "A most tragic thing happened. I met a richer old man."

The case history of a woman with bronchial asthma revealed that she had been frequently hospitalized for periods of a month or more. She had been advised by her physician to stay at home, night after night, until she wanted to scream with boredom. She had submitted to this social deprivation because of feelings of guilt which she had experienced because she had married a rich man. Subsequently aware of her motivation and needless conscious anxiety (because she also loved her husband), she began to entertain. Outgoing by temperament she resumed gratifying relations with her friends and manifested her social prowess. Soon the hyperventilation from which she had suffered, and which had accounted for exacerbations of mild to severe asthma, was no longer present. There was no recurrence of severe asthma, and she lived for many years thereafter.

Enhancement of capacity for exercise. In some patients with chronic pulmonary disease, inhalation of oxygen has been employed to facilitate physical exercise; a program of graded athletic training with the help of oxygen has ultimately improved the capacity of these patients to extend the range of their activities in many ways formerly not possible for them (5). This disease is characterized by a conspicuous lack of oxygen, the main cause of the symptom of breathlessness.

Enhancement of the capacity for physical exercise, as well as the beneficial effect of restoration of physical fitness, has been observed in nearly 100 cases in which exertional dyspnea had previously accounted for excessive precautions to avoid physical activity.[1] In patients with diffuse obstructive pulmonary emphysema, the increased ability to walk when inhaling 40 per cent oxygen was in part made possible by a marked lowering of the pulmonary ventilation induced by the oxygen. This "training" reaction to enhanced physical activity was characterized by a decrease in the pulse rate with exercise, as well as a lowering of the minute volume of respiration.

Concepts of illness. Lack of vitamins was shown to be a cause of disease by studies on the effect of diets deficient in thiamine chloride, and studies on the cure of beriberi. Thus, to the usual concept of illness arising from toxic substances, bacteria or degenerative processes, was added the concept of illness arising from a deficiency of a dietary vital factor. Subsequently, disturbances of bodily and mental function were traced to lack of other substances necessary for

[1] A more complete account of the principles, techniques and results of the oxygen exercise program will be reported by Barach, A. L., in *Anesthesiology*, June 1961, and by Beck, G. J., Bickerman, H. A., and Nanda, K., in a paper to be presented at the annual meeting of the American College of Chest Physicians, New York, June 25, 1961.

normal physiologic and psychologic behavior, such as protein food, electrolytes and enzymes. F. G. Hopkins of Cambridge, England, named this type of disorder "disease with a minus sign" [quoted by Galdston (6)].

The concept of disease with a minus sign has been extended to man's psychic functions; it has been recognized that the neuroses are not simply caused by unconscious conflicts. Deprivation of adequate experience in living may play as significant a role in producing neurosis as it does in aggravating disorders of the cardiorespiratory and nervous systems.

Psychotherapeutics. Stimulated by the remarkable success that followed Ferenczi's treatment of the severely ill psychoneurotic patient, physicians in the field of psychotherapeutics have embarked upon a courageous use of the relationship between doctor and patient, including the willingness at times to provide affection as well as insight when it appears advantageous to do so. Freud long ago reported that ill health may sometimes originate in part from the unkindness of parents, and that a remedy may be found in transferring the image of the father to the analyst.

Unfortunately some psychotherapists have veered backward to the belief that the frustrated person will be better off if he relinquishes all impulses not socially sanctioned by contemporary society. Instead of utilizing the insight that has been gained about the unconscious mind, as well as conscious conflicts, these psychologists often advocate superficial suggestive therapy, such as the gospel of loving everybody, of merging with the infinite, or some similar "higher" order of social relatedness of an impersonal nature—in essence, a peaceful sublimation of man's natural inclinations—in order to obtain a superficial serenity. However, Marcuse (7) pointed out that the outcome of this program is often the development of distress, mental or physical, or the warping of character by the acceptance of deprivation as a fee which, though it minimizes anxiety, results in what has been described as the non-suffering, character-defect type of personality.

The divergence in advice which physicians may offer represents a fundamental conflict between those who emphasize the validity of personal freedom and those who preach conformity to the moralistic code of an authoritarian culture. Naturally, all grades of compromise between these points of view are present in our society.

Recently Bronowski (8) recommended that the scientist be called upon to formulate a new gospel of morals, since men of science may accept no absolute values but instead the dictum that a theory, to be accepted as truth, must work. His stimulating belief that a less repressive civilization is required in order to prevent world destruction has also been expressed by Meyer (9), Murray (10) and others. A more contented world society, as well as a happier individual, is the justification for urging emphasis on extending the boundaries of personal experience.

It seems appropriate to take a new look at the problem which faces older people today, particularly those with chronic disease who have been subjected to ultra-cautious medical counseling. The content of this essay has wandered

from the so-called physical to the so-called mental, but the aim throughout has been clearly in favor of lifting the limitations which too often handicap legitimate goals of activity.

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A CO-ORDINATED APPROACH TO THE GERIATRIC PROBLEM*

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The geriatric patient, that is, the patient 60 years of age and older, has become one of the greatest medical problems of our time. With life expectancy increasing, the numbers of geriatric patients in all branches of medicine continue to increase. This increase is seen particularly in state mental hospitals, where geriatric patients represent more than 40 per cent of all patients. During 1957 and 1958, about 30 per cent of all new admissions to state mental hospitals in the United States were of patients past 60 years of age. Many of them are retained for a long time.

According to the Federal Council on Aging (1959) (1), veterans of World Wars I and II in civil life number 22,666,000. By 1964, it is estimated that 2,106,000 World War I veterans will be 65 years of age or more. Usually 1 of every 2 veterans with a nonservice-connected psychiatric condition is cared for by the Veterans Administration. The number of patients increases with age: in the age group 55 to 64 years, 55.2 per cent of veterans are under V. A. care. When veterans reach the age of 65 or more, 58.6 per cent are hospitalized in V. A. hospitals. According to the census (May 1960) at Coatesville, 37.4 per cent of patients are veterans of the first World War and are past 60 years of age. We expect an increase in the elderly psychiatric, neurologic, and medical patient population as time goes on.

For psychiatric hospitals, geriatric patients are of special importance because of the problem involved in their discharge from the hospital and rehabilitation in their family circle and their community.

The geriatric patient represents a biologic and psychologic unit as well as a sociologic one (2). Therefore, only a co-ordinated approach, taking into consideration biologic, sociologic and psychologic aspects, will help in solving urgent and important problems in geriatrics.

BIOLOGIC ASPECTS OF AGING

Great progress has been made during the last ten years in research exploring the biologic aspects of aging. Himwich and Himwich (3) have stressed the fact that, after 40 years of age, the basal metabolic rate gradually falls, the decrease being more rapid after age 80. They observed in old age a gradual increase in the water content of the body at the expense of solid elements. The brain appears to shrink; in both the white and gray matter of the cerebral cortex there is an ac-

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cumulation of moisture in old age. The Himwiches believe that the increase in water, along with changes in morphology, may account for mental impairment in elderly persons.

From extensive studies of chemical changes in the brain of elderly persons, Buerger (4) concluded that in old age the protein content of the brain is diminished—especially with respect to glutamic acid, glutamine pyruvic acid, and alpha-ketoglutamic acid. Himwich and Himwich (5) have presented evidence indicating that substances containing nitrogen and phosphorus are diminished, whereas substances containing sulfur are increased.

Kety (6) believes that a loss of neurons, progressive deterioration of certain essential cellular components, and a decrease in neuronal interconnections and interactions are important in inducing the aging process. According to him, the distinct fall in the circulation and the oxygen supply to the brain during the transition from childhood to old age is the basis of all the other chemical, biologic and functional changes.

The importance of the decreased basal metabolism in elderly persons has been confirmed by Shock (7). He believes that the reduction in total metabolism reflects a reduced number of metabolizing units (cells) in the organism.

Lansing (8) points out that the older person is prone to accumulate fat, his physical capacities are reduced, his vision deteriorates, and he lacks adaptability to environmental changes. Lansing believes that calcium may play an important role in establishing the aging process, because it can lower cell permeability.

Gerard (9) relates the phenomena of aging especially to the nervous system, since the neurons decrease in size, the metabolic rate decreases, the cells carry more products of decay, and calcium accumulates and slows the function of the cells. In this way, further growth and fiber formation become impossible. Aging, he believes, is due to failure of regenerative, reconstructive and rejuvenating processes.

Freeman (10) studied the influence of endocrine substances on the aging body and observed that ACTH production may decrease with age. Generally, however, gonadal failure was the only endocrine alteration found to be characteristic of old age.

Summarizing the results of these studies, aging is accompanied by the following changes: 1) an increase in connective tissue throughout the organism, 2) a gradual loss of the elastic properties of connective tissue, 3) disappearance of cellular elements in the nervous system, 4) a reduction in the number of normally functioning cells, 5) an increased amount of fat, 6) a decrease in oxygen utilization, 7) a decrease in the amount of blood pumped by the heart under resting conditions, 8) a decrease in the maximal amount of air expired by the lungs, 9) a decrease in muscular strength, 10) a subnormal secretion of hormones, especially by the gonads and adrenal glands, and 11) a gradual increase of body water at the expense of the solid elements.

Biologists also have given much thought to the higher incidence of arteriosclerosis in populations whose diet is high in fat, and to the theory that a reduction in dietary fat protects against arteriosclerosis. Saturated fats from animal

sources appear to play a greater role in the development of arteriosclerosis than do unsaturated fats from vegetable sources. According to insurance company statistics, overweight in adults reduces life expectancy. An inadequate intake of proteins, minerals, and vitamins also appears to play an important role in reducing the life span. Old people apparently are prone to consume disproportionately high amounts of carbohydrate, due perhaps to poor dentition.

All of these important biologic, biochemical and physiologic studies have been used as the basis for improvement in the treatment of geriatric patients. Therapeutic trials, however, with dietary and pharmaceutical agents (vitamins, endocrine products, glutamic acid, procaine, and other substances) have induced only temporary improvement and have had no definitive value either in prevention or cure.

SOCIOLOGIC FACTORS IN AGING

Sociologic factors influencing the aging process derive from stresses connected with the elderly person's occupation, environment, family and community, which are conducive to a disturbed emotional equilibrium. Among them, retirement is perhaps the most important.

Retirement is the factor that most frequently causes emotional upsets leading to the hospitalization of elderly people. When older persons have acquired no hobbies and interests in earlier years with which to occupy their time and their minds after retirement, they are unable to relax and enjoy life. Too much leisure makes them feel useless and superfluous; therefore they concentrate their interest on physical illness, and this gives rise to psychosomatic complaints and depression. Retirement often causes a severe loss of self-esteem. To lose one's goal in life means for many old persons the end of hope and of life itself. Many old people have for years held their minds and bodies together by compulsive work. Unused to relaxation and not knowing what recreation means, in later life they undergo a complete breakdown of physical and mental health, instigated by sudden and severe confusion and disorganization. They are "lost" in the true and symbolic sense of the word.

Elderly persons must not only retire from something, but have something to retire to. To find suitable hobbies and interests for them, to make them relax and feel less anxious, and to help them "recreate" a new life is one of the most important goals of preventive treatment for aged persons.

The second factor with great influence on emotional and physical health is our *cultural attitude toward the aged*. This is the "century of the child and the youth." We are directed toward social and economic goals and driven by an irresistible force to achieve them. We live in a world of continuous competition and have to work compulsively and strenuously to be able to take a place or to hold one. We are in a continuous state of anxiety and tension, and decide that "time is money." We are overburdened with work and have no time for recreation or relaxation, sometimes not even for sleep. We lose connection with Mother Nature and with the rhythm of life. Music, art and literature are considered a "waste of time." There is no relaxation in family life, nor in love. Sexuality

frequently takes the place of true love, and the responsibilities of family life make us worry day and night. We live without imagination, play, fantasy or romance. We sometimes lose the feeling of being human beings and do things mechanically and without interest. Then, as the end of life approaches, we are exhausted and feel that we have not really lived. In such a world of tension, compulsion, work and competition, elderly people are considered a burden. They know it, feel it, see and hear it, and are unhappy and dejected. Elderly people cannot compete with this trend, but they are unable to change it. We however, can and should do something about it.

Linden (11) points out the link between our lack of respect toward elderly persons, our cultural attitude of rejection and intolerance, our feelings of impatience, hostility and annoyance with elderly parents or grandparents, and the increase in juvenile delinquency. Children who cannot identify with father or grandfather, who consider elderly parents useless and burdensome, who laugh about senior citizens, and who grow up without parental support and ethical judgment, are frequently in a state of rebellion. When life experience and wisdom are held in no esteem, when parents and grandparents are not examples of goodness and personal worthiness, when authority is rebelled against because it is not considered, we create an atmosphere of freedom without limits, of wanting without boundaries, and of egocentricity. When a child does not learn to look upon the elderly person as an object of respect, the door is open for rebellion and disobedience. Police control never can substitute for parental support. Punitive measures never will be as effective as parents' love and understanding. Linden concludes that our cultural attitude is partially to blame for the increased delinquency of our children—children who have not learned from us the true values of life.

The third consideration is the feeling of *economic insecurity* from which so many old people suffer. Old people need to live protected from physical and emotional sickness and from the most urgent needs of daily life. Public Welfare will help when the need arises, but this help should be given willingly and effectively in order not to cause an emotional blow and severe loss of self-esteem. Special housing projects, hospitals for the chronically ill, and rehabilitation and recreation centers need to be built. Only in this way can we prevent many emotional and physical illnesses of elderly persons. The accent, however, should not be on welfare but on rehabilitation. Most elderly persons still can do useful and meaningful work, provided they find understanding for their problems. They may work more slowly than younger persons, but they may be able to work with great exactness. In Switzerland, for instance, many older people are watchmakers because of their greater experience and patience. In America, to a limited extent, we are using the skills of elderly persons as furmakers, tailors, and even machinists. In politics, art, philosophy and science, despite old age, Churchill, Ghandi, Toscanini, Einstein, Albert Schweitzer, Grandma Moses, and many others have been able to create things of which all humanity is proud. We need not take a pessimistic attitude toward elderly persons. They need not regress, deteriorate, become useless, or be considered superfluous. They can offer things

younger persons do not possess: wisdom, patience, and life experience which should and can be utilized for the benefit of all of us.

PSYCHOLOGIC ASPECTS OF AGING

The emotional needs of the elderly person recently have been described by a number of outstanding physicians and psychiatrists. It has been stated that the cause of mental breakdowns in later life frequently can be found in experiences during childhood and adolescence. Early experiences do play an important part in the origin of schizophrenia and manic depressive psychosis. We have come to recognize that mental disturbances such as involutional psychosis and senile dementia also have their roots in childhood experiences. Grotjahn (12) ascribed the extreme restlessness sometimes found in geriatric patients to the castration fear from which they have suffered throughout their lives. I have been able, by means of sodium amytal interviews, to confirm this idea, and frequently have found a connection between the fear of death and castration anxiety—death being considered the final castration.

The irritability of older psychotic patients often has its source in inability to cope with the environment, as well as in physical decline. Apathy in elderly persons can be considered an outcome of their detachment from painful memories and events in life. Kaplan (13) states that one of the effects of losing friends and relatives is to give the older person not only a feeling of being alone in the world but also a feeling that, without social ties, he is unprotected and insecure. Overholzer (14) is of a different opinion and suggests that our attitude of overprotection toward old people results in personality change. He believes that we should be careful not to accelerate their entrance into dependent helplessness. Loss of independent activity frequently produces an emotional crisis. For instance, retirement gives more opportunity for introspection, self-evaluation, the development of delusional ideas, and regrets. Older men, who tend to be more seclusive and withdrawn than older women, are more inclined to cerebral arteriosclerosis, whereas women suffer more from senile dementia.

The problem of growing aware of being old has been studied by Jones (15) and others. Subjects have been asked how and when they noticed for the first time that they were growing old. In most cases, the following symptoms were mentioned: 1) breakdown of locomotor apparatus, 2) difficulties of a nervous variety, 3) sense-organ impairment, 4) deterioration of the skin and hair, 5) an increased tendency to fatigue, and 6) a greater need for short periods of sleep during the daytime.

Paranoid trends become more evident in senile persons when their personality traits have been of a suspicious nature. Old people often feel unwanted, and this realization may be conducive to delusional ideas. Frequently, the content of the delusion centers around the idea of being robbed, poverty stricken, or poisoned. There is an increased tendency to commit suicide in the higher age groups. The loss of loved ones or physical sickness with a poor prognosis may augment this tendency and must be given careful consideration. Criminal offenses generally decrease with old age. However, sexual offenses, fraud, the

violation of narcotic laws, arson, and poisoning are common reasons for bringing older people to court and, afterwards, to mental institutions. Studies of the emotional needs of the elderly have been made by comparing their attitudes with those of children. A child has unlimited energy, great ambition and psychic elasticity; these help to keep him from being hurt. He reaches out for the future. The aged person finds his supply of energy diminishing. He fears the future, is blind to reality, and remains in a continuous state of disillusionment.

Meerloo (16) defines the geriatric patient as one who does not, and cannot, accept the reality of being mortal. He considers old age a traumatic neurosis with continuing trauma. The old person becomes more self-absorbed and tests his vital functions continuously. It has been held that diminishing heart function symbolizes a loss of love.

Many geriatric patients have ambivalent feelings toward life and death. They often want to die, believing they have nothing for which to live. They wish for cessation of their physical and mental preoccupations but, when they feel the hour may be near, become disturbed and afraid. They cling to others and want them near at all times. The especially fear the dark and request that a light be kept on at night. They may turn toward religion, go to church often, confess, and ask that their sins be forgiven. Religion gives them emotional support and tends to relieve them from the fear that everything soon will come to an end.

We have treated geriatric patients suffering from emotional disturbances by means of group psychotherapy over a period of many years (17, 18), and thus have been able to study their thought content extensively and make the following observations: Geriatric patients are conservative, sensitive, and emotional. At times an attitude of rigidity, as well as a lack of flexibility with compulsive trends becomes evident. Such behavior appears to be a sign of decompensation, and is a last-ditch attempt to hold the personality together; it is a fight against desperation and the feeling of complete confusion and fear of being lost. When improvement occurs, these symptoms disappear and are replaced by the ability to relax and a decrease in rigidity.

The most frequent topics chosen for discussion by members of the group were: 1) religion, 2) marriage and love, 3) historical events, and 4) food.

Religion was the preferred topic. Unhappy, lonely and despondent patients were eager to discuss a better life after death, in paradise—perceived by them as a haven of love and kindness. The religious attitude increased when the personality disintegrated and became disorganized. Religious belief, that is, faith in God, helped them to overcome their grief.

Nearly all patients were in agreement when the discussion came to problems of love and marriage. They expressed deep attachment to their spouses; they showed anger against them only during the acute phase of their illness. Hostility toward their children was a more frequent topic for debate. Resentment, disappointment, hate, and a feeling of being rejected and regarded as a burden by the younger generation were discussed.

Another favorite subject of conversation was historical events. The patients liked to talk about kings and queens of the countries of their family's origin, the early settlements of the United States, religious and political customs of fifty or

more years ago, the Spanish American War, and famous poets and artists. Technical progress, the automobile, the telephone, modern machinery, and farm equipment rarely were brought into the conversation.

The patients liked to read books about the Civil War in the United States and showed a rather conservative inclination toward the problem of racial discrimination. At times, they were not particularly tolerant. They appeared to be threatened by revolutionary ideas and occasionally showed ambivalent feelings toward new immigrants. Newcomers who did not speak English were not readily accepted at the beginning, but as time went on they found better understanding and sympathy and formed friendships with the other participants in the group.

Unless physically sick, these geriatric patients liked to eat and showed a certain degree of regression to the oral stage. Consequently, one of the most important topics of discussion during the meetings was food. Candies and chocolates were exchanged. The meals on holidays and at birthday parties (including cookies and cakes) were often mentioned. Stomach trouble due to overeating was a common occurrence.

For elderly patients, great preoccupation with eating or digestive problems is not a favorable symptom. It can be considered a regression into the infantile, immature and dependent state, and this may be reinforced by an overprotective attitude on the part of relatives or attendants. For some patients, this kind of regression towards excessive oral cravings may become a serious handicap to treatment and release from the hospital.

Intellectual changes in old people were studied by Miles (19) at Stanford University. He found that imagination seems to be ageless, whereas verbal associations, interpretations of meaning, and recognition of relationships show less tendency to decline with aging than do speed, organization, recall of unfamiliar material, and difficult logical procedures. The total intelligence quotient scores indicate a progressive decline with advancing age. Wechsler (20) pointed out that a parallelism exists between curves showing loss of brain weight with aging and those showing decline of ability with aging. Gitelson (21) and Gilbert (22), however, believe that motivation to keep healthy, mentally and physically, is an important factor in guarding against intellectual decline.

Birren (23) made special studies regarding changes in sensation, perception and learning. He observed that with advancing age there is an increased delay in all voluntary responses. The older organism seems to require additional time to integrate or perceive information from the environment and to "program" the appropriate response. These longer latent periods appear to have their greatest consequence in complex or serial tasks. The inference is drawn that the capacity of the central nervous system to integrate complex activity is limited. However, the high redundancy of our verbal and social skills tends to mask the development of changes in the central nervous system with aging. Generalizations, according to Birren, must be avoided.

SUMMARY

Our knowledge of the various aspects of aging is limited. More and more physicians and psychiatrists are becoming aware of the geriatric problem and

are working to extend our knowledge. An approach that takes into consideration the biologic, sociologic and emotional factors in aging will furnish the means to satisfactory management, therapy and rehabilitation of elderly persons.

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ACCURATE COMPARISON OF ELECTROCARDIOGRAPHIC PRECORDIAL LEAD PATTERNS

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Electrocardiographic standard and unipolar limb leads demonstrate practically identical patterns when recordings are made at various intervals in the same patient in the absence of acute myocardial disturbance or change in body position. When attempting to compare serial precordial lead patterns, however, this advantage is lost, since often the placement of the precordial electrodes varies from one tracing to the next, with concomitant variations in the R/S ratios and T-wave amplitudes.

In order to eliminate this disadvantage, we have used a solution for marking the skin over the precordium. This facilitates the accurate recording of sequential precordial patterns in which the R/S ratios and T-waves do not vary in the absence of myocardial change. The solution was originally proposed by Allen *et al.* (1) for use in marking skin areas overlying varicose veins in the lower extremities. The formula is as follows:

Pyrogallic acid	5 Gm.
Acetone	50 ml.
Solution of ferric chloride (N. F.)	40 ml.
Ethyl alcohol, to make	100 ml.

(Dissolve the pyrogallic acid in alcohol; add acetone and ferric chloride solution, and alcohol to make 100 ml.)

When the electrode is placed on the marked areas (V-1 to V-6), accurate sequential recordings are obtained in any specific case.

This marking solution remains readily visible on the skin for more than a week despite vigorous washing. It may be easily applied with a cotton applicator. It is also quick-drying, nontoxic, not disfiguring, not affected by electrode paste, and inexpensive.

In this manner, one can avoid the pitfall caused by the false impression that, owing to the "appearance" of Q-waves, there has been an extension of myocardial infarction. The technique is also of value in the detection of RST and T-wave changes in the serial precordial leads.

An example of factitious Q-waves in lead V-3 is presented in Figure 1. Figure 2 shows an example of identical R/S ratios in the precordial leads in a patient on whom the marking solution was used. In contrast, Figure 3 shows the sequential electrocardiograms in á patient in whom the precordial lead recordings were first made in the usual precordial positions V-1 to V-6 and then 2.5 cm. lateral to these positions.

* Assistant Professor of Medicine.
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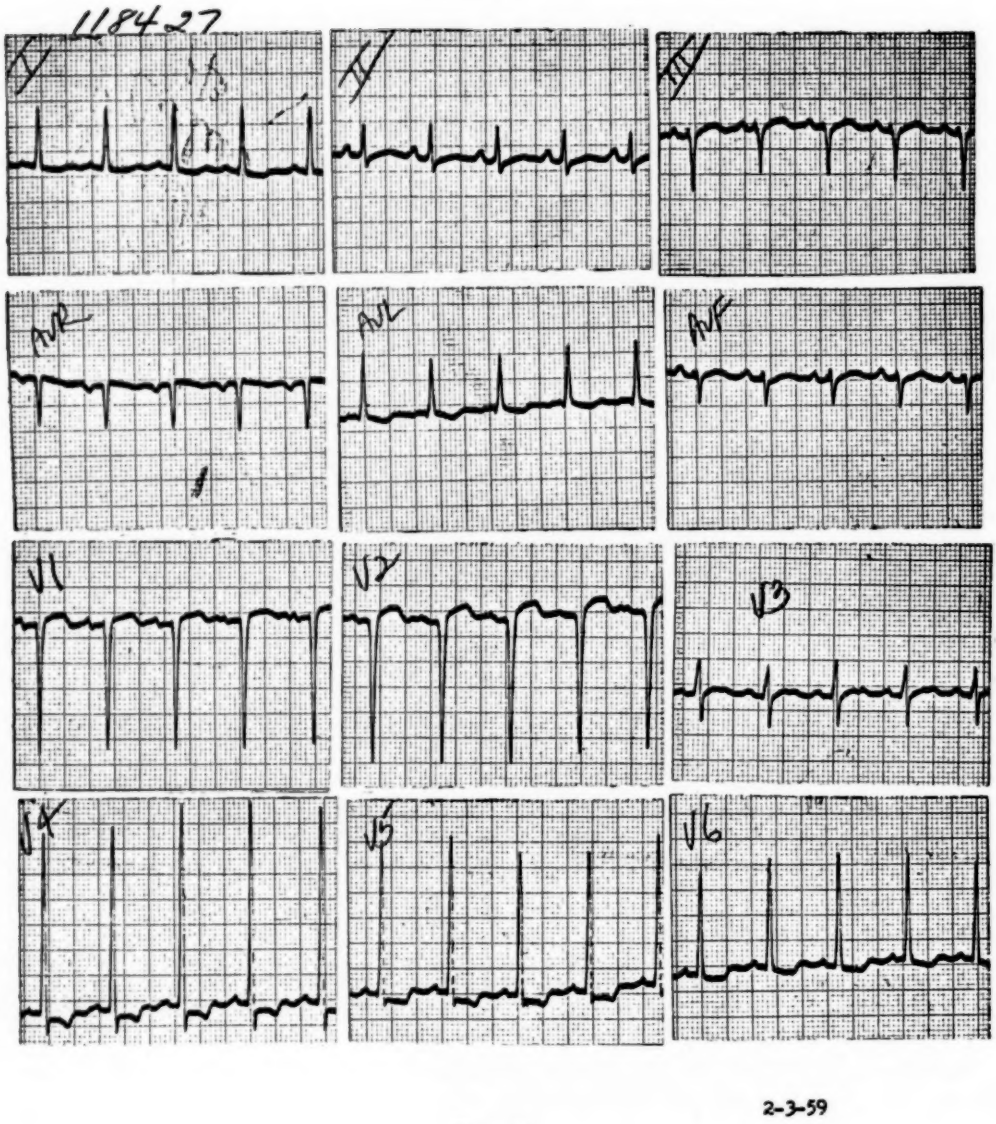

FIG. 1A

FIG. 1. Patient J. C. (#59-58730): Anteroseptal myocardial infarction with factitious Q-waves in V-3 and subsequent "reappearance" of tall R-waves in that lead, due to changes in placement of the electrode in V-3 position on the successive dates noted (Sections A, B, C, D and E, respectively).

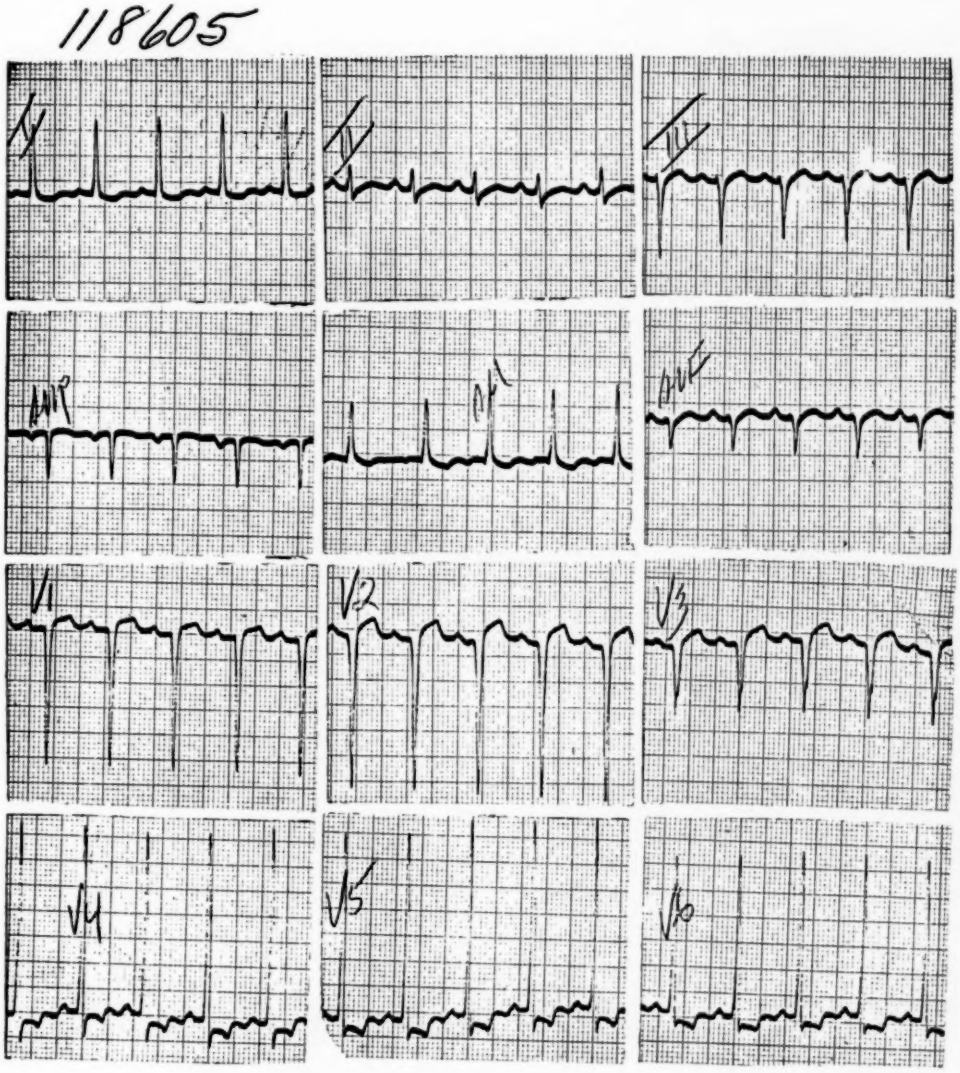

FIG. 1B

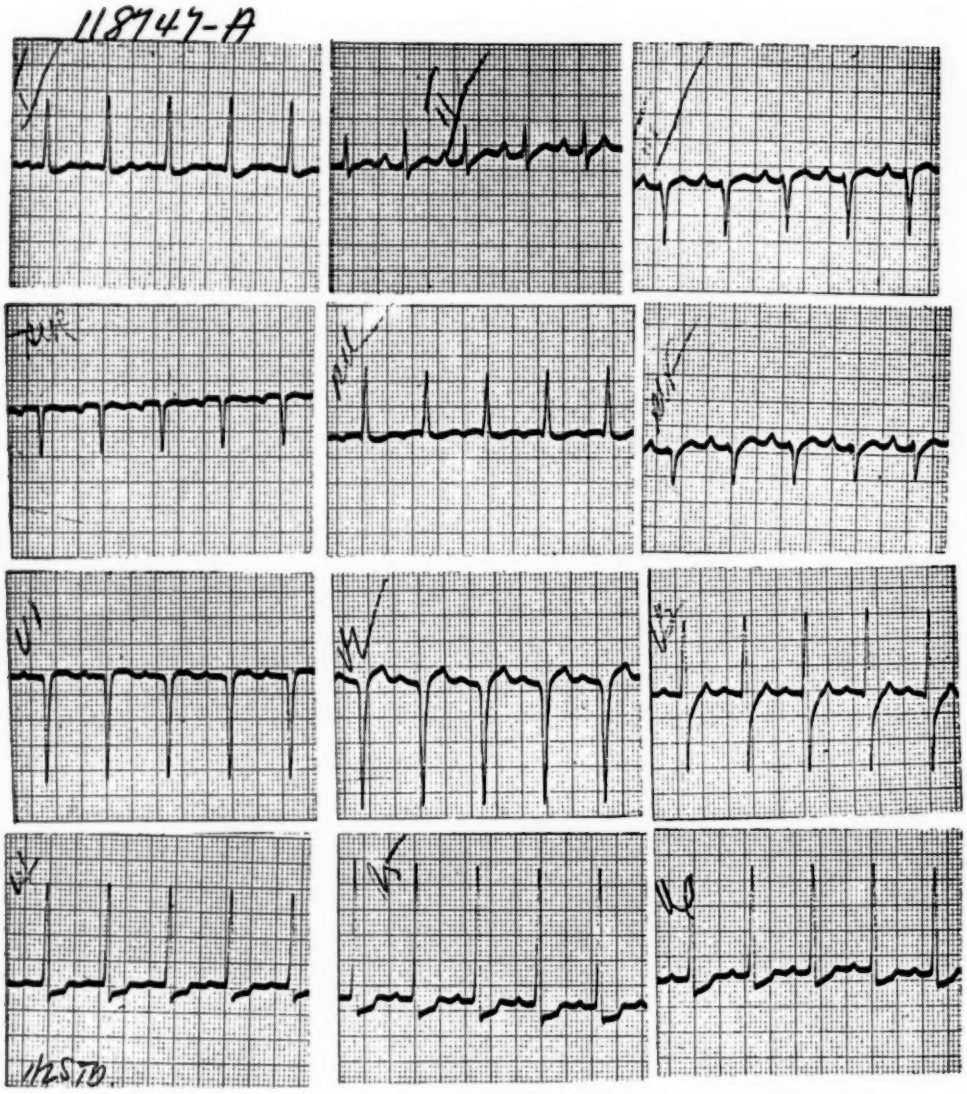

FIG. 1C

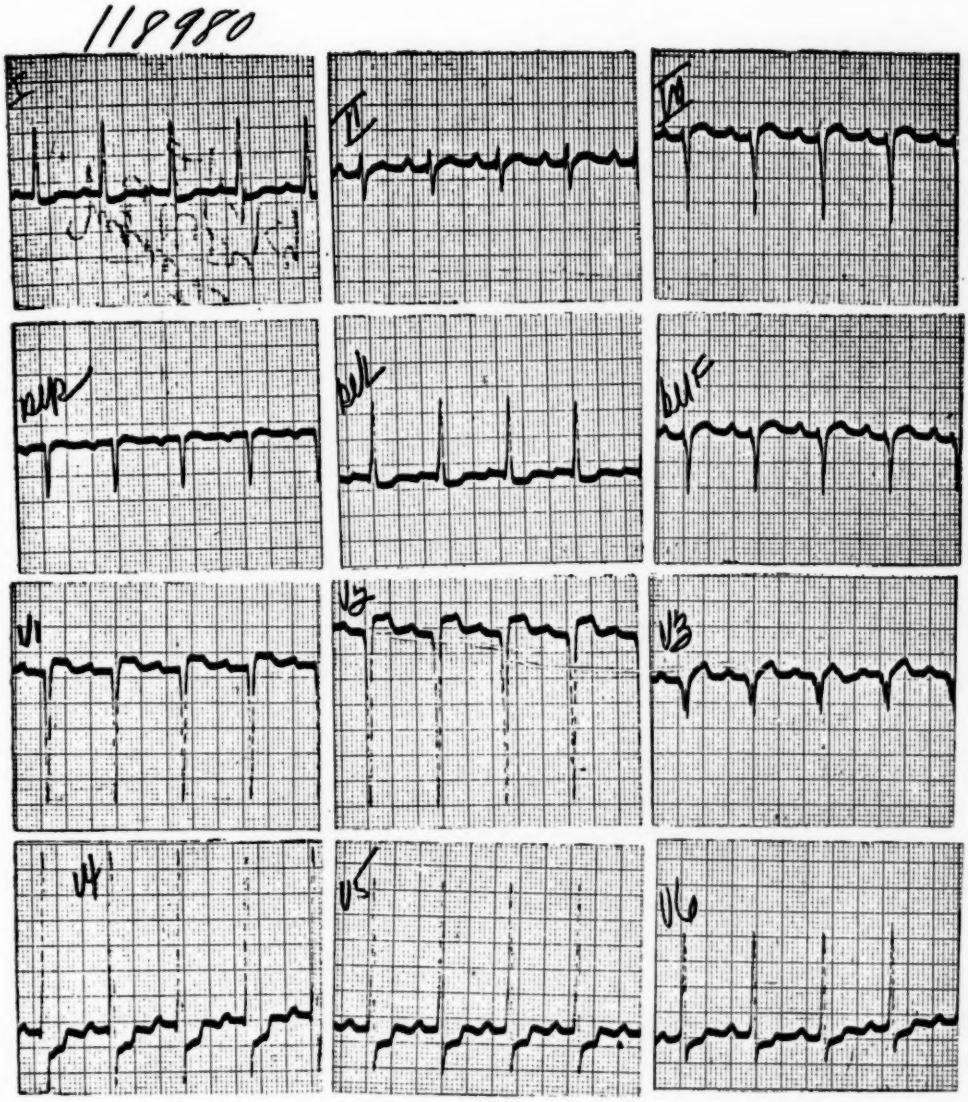

FIG. 1D

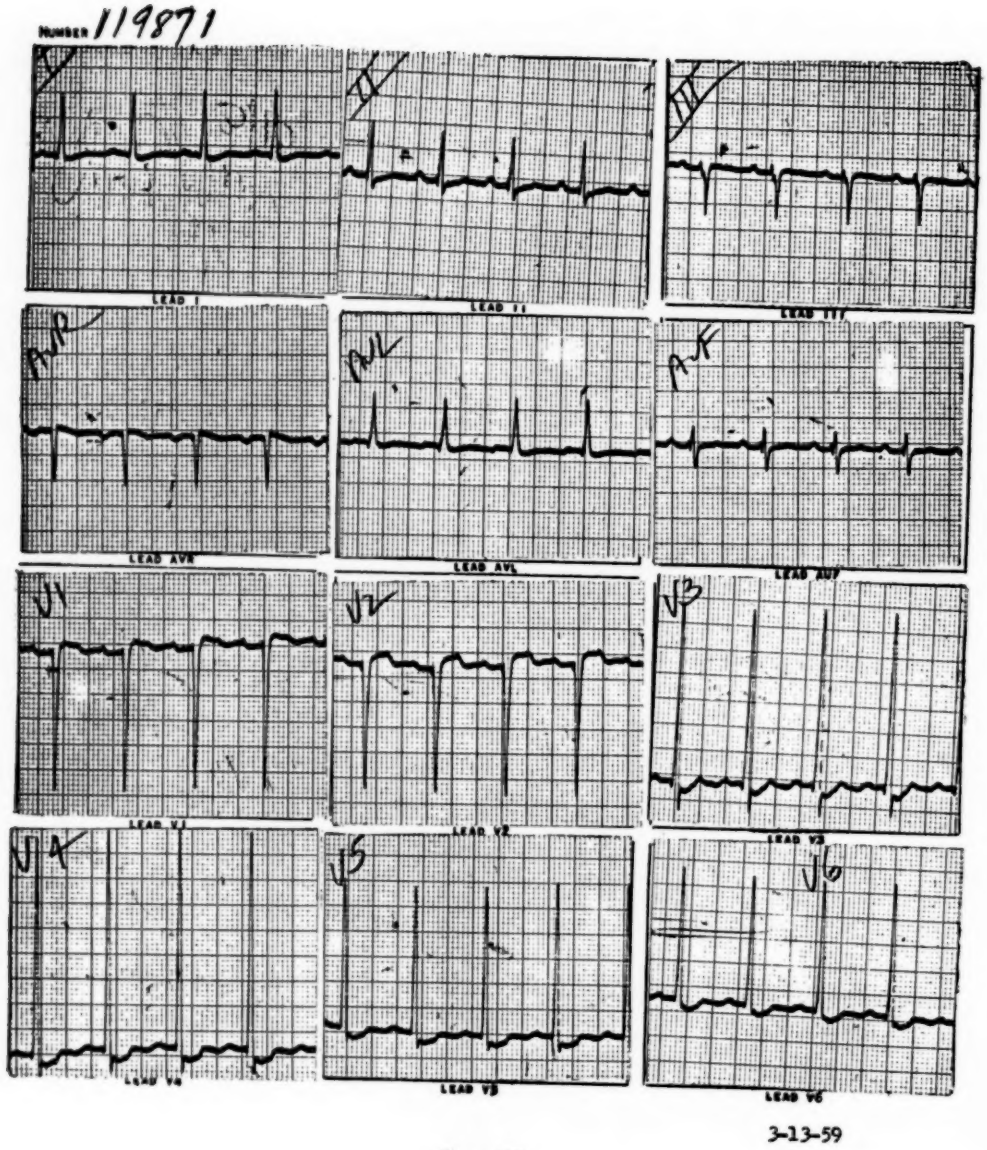
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FIG. 1E

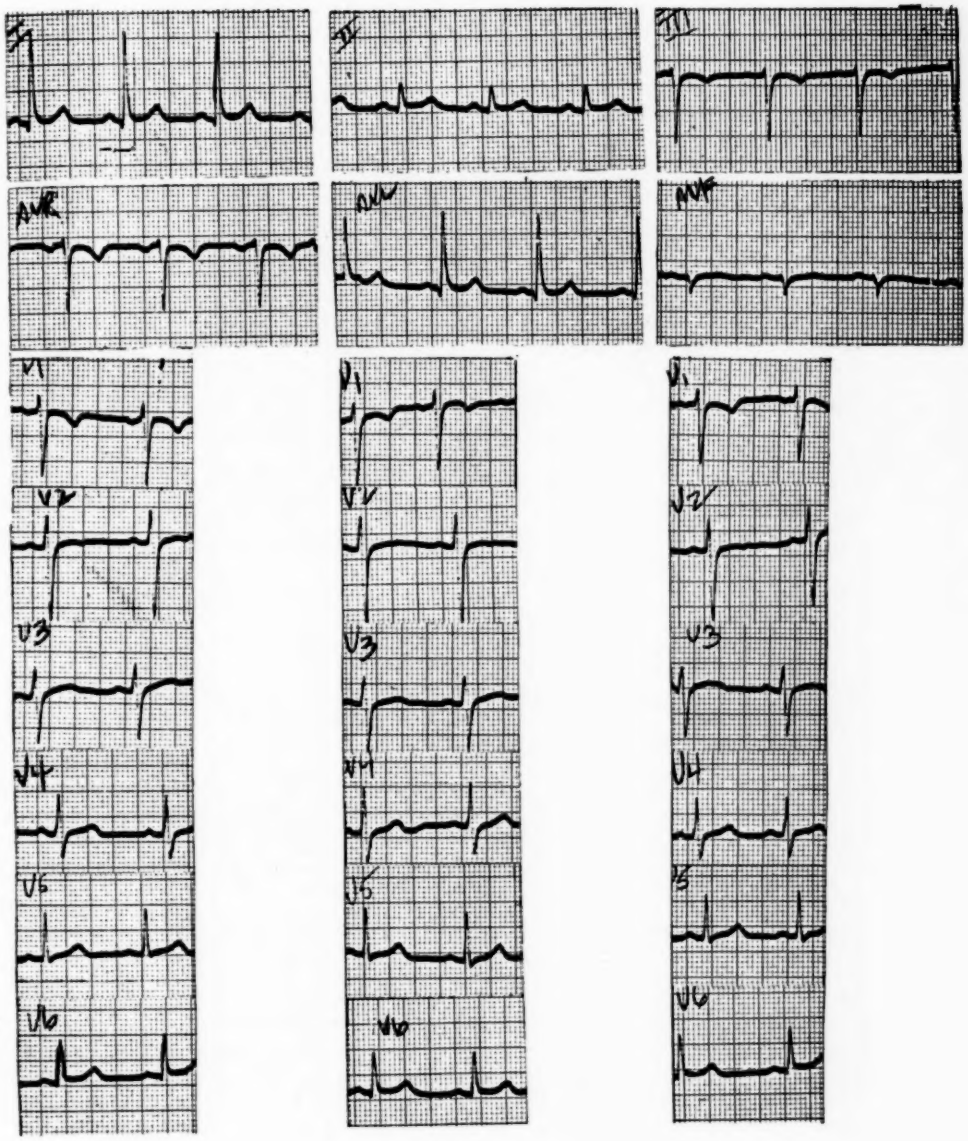

FIG. 2. Sequential precordial leads in a patient in whom skin-marking solution was used in V-1 to V-6 positions. R/S ratios were practically identical.

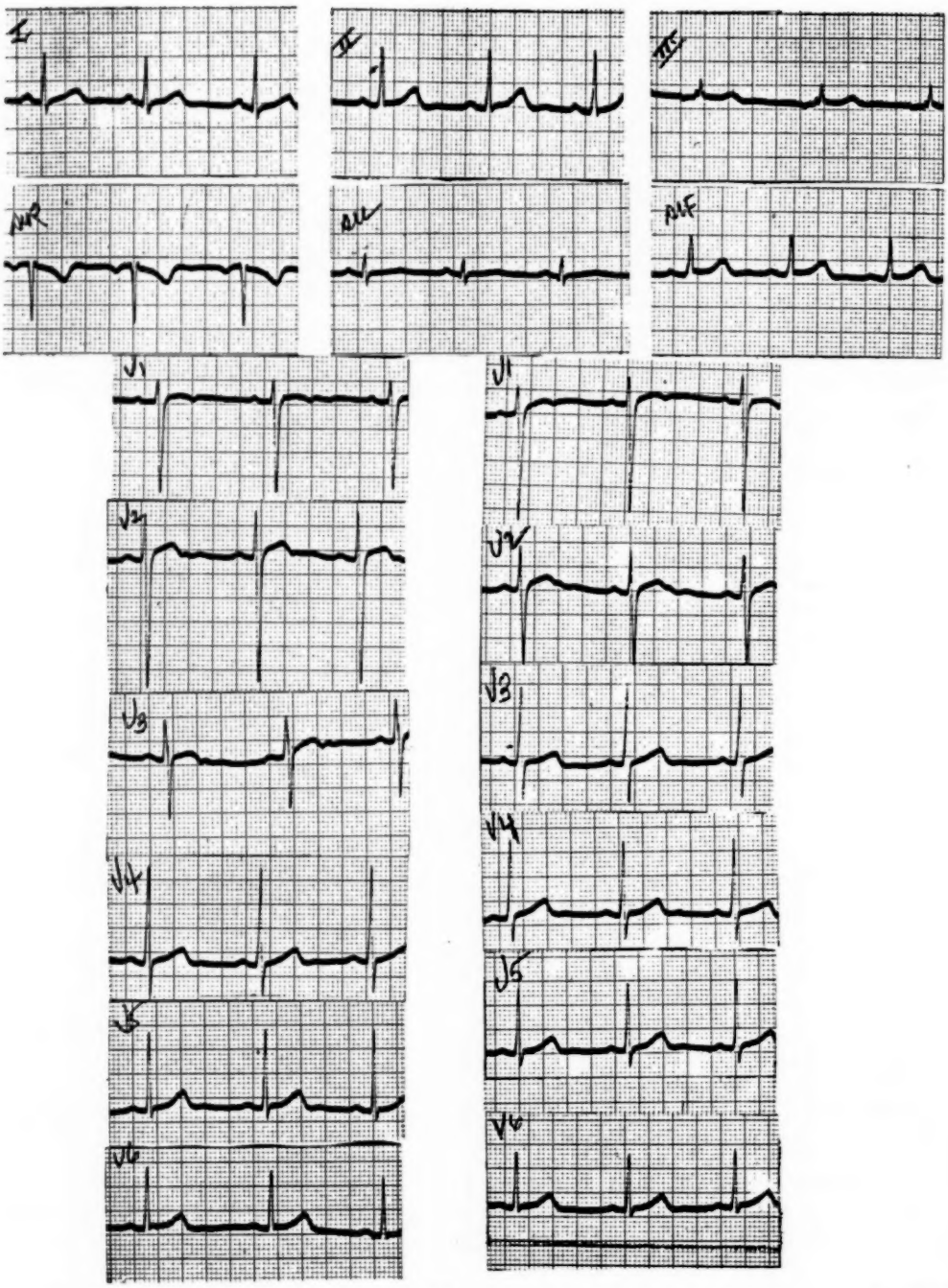

FIG. 3. Precordial lead patterns within normal limits, but R/S ratios not identical owing to change in position of placement of electrodes.

SUMMARY

A method is presented by which the electrocardiographic patterns obtained by means of sequential precordial leads may be compared accurately.

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1. ALLEN, E. V.; BARKER, N. W., AND HINES, E. A., JR.: Peripheral Vascular Disease, ed. 2. Philadelphia, W. B. Saunders Co., 1955.

BASIC PERSONALITY TRAITS CHARACTERISTIC OF PATIENTS WITH PRIMARY OBSTRUCTIVE PULMONARY EMPHYSEMA

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INTRODUCTION

Many investigators have attempted to assess the role of psychologic factors in chronic disease. Since chronic obstructive emphysema is becoming increasingly important among the diseases affecting our aging population, a study of a homogeneous group of patients with this condition seemed pertinent. As far as we can determine from a review of the literature, no such report has hitherto been published. There are, however, studies (1–5) showing that bronchial asthma is often associated with such traits as hypersensitivity, marked passivity, effeminateness, emotional immaturity and a feeling of insecurity.

In many cases of bronchial asthma, chronic obstructive emphysema is present as a complication. Unfortunately, in most published reports there is no differentiation between this secondary emphysema and primary emphysema not related to bronchial asthma. Thus the crucial selective criteria were not taken into account.

SELECTIVE CRITERIA FOR OBSTRUCTIVE EMPHYSEMA

In the longitudinal study of emphysema which has been in progress at the Research Service of this institution for the past several years (6), the following classifications have evolved:

1. Acute obstructive emphysema associated with periodic attacks of extrinsic bronchial asthma.
2. Chronic obstructive emphysema secondary to repeated attacks of extrinsic bronchial asthma.
3. Chronic obstructive emphysema associated with, and secondary to intrinsic bronchial asthma.
4. Primary obstructive emphysema with cough, bronchitis and production of sputum.
5. Primary obstructive pulmonary emphysema without cough, bronchitis or production of sputum.
6. Obstructive emphysema as part of the pulmonary fibrotic process secondary to:
   a. silicosis, asbestosis;
   b. phosgene and other gaseous poisons;
   c. radiation pneumonitis, lipoid pneumonia;
   d. tuberculosis, fungus infection;
   e. acute or chronic intercostal fibrosis.

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TABLE 1

Age Distribution of Patients in Emphysema and Control Groups

Age Group (yrs.)	Domiciliary Groups				European Group	
	Emphysematous (33 patients)		Non-emphysematous (43 per patients)		No.	Per cent
	No.	Per cent	No.	Per cent		
40–49	1	3.0	0	0		
50–59	4	12.0	8	18.5		
60–64	16	49.0	15	35.0		
65–69	7	21.0	14	32.5		
70–90	5	15.0	6	14.0		
61–70					200	100
Total	33	100.0	43	100.0	200	100

7. Obstructive emphysema caused by a foreign body, tumor or aneurysm, within or without the bronchial tree.

CLINICAL MATERIAL AND METHODS

The patients

The present report deals exclusively with 33 intensively studied patients in a Veterans Administration domiciliary, all of whom had primary obstructive emphysema (groups 4 and 5 in the foregoing section). The age distribution is shown in Table 1. For 28 of the 33 patients, the age range was 60–90 years. They were chosen after the following procedures had been carried out:

1. An anamnesis, including information regarding nativity, residence, occupation, smoking habits and a history of the respiratory symptoms.
2. A special physical examination of the chest with estimations of chest wall movement, mobility of the spine, use of accessory muscles, height and motility of the diaphragm, intercostal hypertrophy, presence (and degree) or absence of reversible bronchial obstruction, and the status of the circulation.
3. Test of exercise tolerance.
4. Estimation of time and total vital capacity with the portable McKesson-Scott apparatus.
5. Pulmonary function studies, including timed and total vital capacity, maximal breathing capacity, volume of residual air, speed of mixing, analysis of respiratory gases for oxygen and carbon dioxide and analysis of blood for oxygen saturation, carbon dioxide content and pH.
6. Fluoroscopic examination of the chest.
7. Inspiratory and expiratory chest x-ray films for measurement of diaphragmatic height and movement.
8. Daily examination of the sputum for physical characteristics and microscopic study of the cells.
9. An electrocardiogram.
10. Skin tests with common allergens.

Controls

The control groups (Table 1) comprised: 1) a random sample of 43 nonemphysematous males drawn from the same domiciliary population as the emphysema group and comparable

TABLE 2

Marital Status of Persons More Than 21 Years Old

Group	Percentages	
	Married or widowed	Unmarried or separated or divorced
Emphysema (33 patients)	30.3	69.7
Domiciliary controls (43 patients)	35.0	65.0
General population (U. S. Census)	66.2	33.8

with respect to sex and age; and 2) a normal group of 200 Europeans between the age of 61 and 70, as studied by Szondi (7).

Plan of study

The study of the emphysema group and the domiciliary control group was conducted by means of: 1) the personal and familial history (anamnesis) of symptomatic behavior, and 2) depth psychologic procedures.

BEHAVIORAL ANAMNESIS

Marital

Only 10 of the 33 emphysematous patients were either married or widowed; the remaining 23 were either unmarried, separated or divorced. As shown in Table 2, the marital statistics were in marked contrast to those for the general population. Although marital instability (unmarried, separated or divorced) was approximately the same among the domiciliary controls as among the emphysematous patients, it was noted more than twice as often among the emphysematous group as among the general population.

Correlates of morbidity

According to Szondian depth psychology, asthmatics belong to the so-called ixoidian personality group as described by Ewald Bohm (8). This category embraces persons with certain epileptiform manifestations. In order to determine whether our primary emphysema patients also belonged to the ixoidian category, individual and familial histories were explored for evidence of syncope, confused mental states, migraine, asthmatic attacks, neurodermatitis, stuttering, enuresis, nomadism and extreme vocational mobility. The results are shown in Table 3. It may be seen that 85 per cent of the subjects studied manifested one or more of the foregoing epileptoid symptoms at some period in their life history, and that more than half had followed a peripatetic occupation.

PSYCHOLOGIC PROCEDURES

Other Studies

One widely used instrument for exploring the psychologic factors of disease has been the Minnesota Multiphasic Personality Inventory (MMPI). This

TABLE 3

Symptomatic Behavior of 33 Emphysematous Patients

Manifestation	Frequency	Percentage
Paroxysmal disorders	28	85
epileptoid	24	73
epileptiform paranoid	4	12
Peripatetic occupations	17	52

device is a refined personality questionnaire which purports to assay psychic life at the conscious level, and from the results of this exploration to compile in each case a so-called personality profile classifiable according to a series of statistically determined psychiatric and psychologic categories. For example, Heiskell *et al.* (9) utilized this test to study a well defined population suffering from bronchial asthma and were able to demonstrate the so-called psychosomatic "V" profile typical of the functional disease classification. Harrower (10) employed the Szondi test to study the personality traits of 61 patients with multiple sclerosis compared with those of control groups comprising 200 emotionally disturbed persons, 400 normal subjects and 70 cases of poliomyelitis and parkinsonism. In this study, and in a later one by Harrower and Kraus (11) relating to 140 cases of multiple sclerosis, statistically valid differences were demonstrated. Petz (12) utilized the Szondi test to determine the personality traits of 52 patients with pulmonary tuberculosis, applying both the factorial and vectorial methods of analysis to the 10 profiles of each patient for a total of 520 profiles. The results enabled her to evaluate the psychic relationships between a group of pulmonary tuberculous patients on the one hand and groups of schizophrenic, neurotic and other patients on the other hand.

The Present Study

The Szondi test was employed because: 1) it apparently reveals subconscious motivations to a greater degree than does the MMPI; 2) it is easier to quantify statistically than a test of the Rorschach type, and 3) it is considered, particularly in Europe, to be a biologic test.

The Szondi test was administered to each subject of the emphysema and domiciliary control groups a total of 10 times, with at least a 24-hour interval between any two administrations. Then, in accord with prescribed procedures, a statistical comparison was made of the factorial and vectorial data gleaned from these two groups, and the available data on the European normal group, which had been gathered by a similar procedure.

SZONDI TEST FINDINGS

Symptomatic reactions

The ratios of symptomatic (± or 0) to radical (+ or −) reactions were as follows: emphysema group 29.7 per cent, domiciliary group 29.5 per cent and

TABLE 4

Dur-Moll Ratios

Group	Dur (M)*	Moll (F)*	Ratio M:F
Emphysema (33 patients)	640	1043	1:1.7
Domiciliary controls (43 patients)	867	1274	1:1.5
Normal (all ages)	—	—	1.5:1.0

* M = masculine; F = feminine.

normal group 20–30 per cent. The patients with emphysema, therefore, did not tend to repress their conflicts nor to reflect them in symptoms, except in certain problem areas described later.

Masculine-feminine ratio

The M:F or Dur-Moll ratio can be estimated by either of two procedures: 1) the original Szondian factorial method, or 2) the vectorial method according to Waltisbuehl.

From the factorial ratios shown in Table 4, it is evident that, in the aggregate, the emphysematous patients were passively oriented to a slightly greater degree than the domiciliary control group, but that both these institutional groups were the antithesis of the normal group with respect to M:F ratio.

The vectorial Dur-Moll ratios were grouped for both the emphysematous and domiciliary control groups and treated statistically to determine whether there was a significant difference between the two groups. As seen in Table 5, the vectorial ratios varied somewhat from the factorial ratios; in the vectorial study the emphysematous group exhibited more passivity. Both domiciliary groups, however, were preponderantly masculine on the vectorial scale. Abnormally accumulated tension in all the factors is interpreted as a masculine manifestation, and both groups showed an unusually great accumulation of tension, particularly in the psychosexual and ego vectors. Normal groups do not show this phenomenon. However, the variability among the members of both groups was so marked as to make the mean ratio unreliable. According to

TABLE 5

Statistical Comparisons of Dur-Moll Indices

(according to Waltisbuehl)

Statistic	*a*. Domiciliary Control Members (N = 43)*	*b*. Emphysematous Members (N = 33)	*a* − *b*
Mean	3.23	4.40	1.17
Median	2.60	1.80	.80
Mode	2.30	2.80	−.50
Sigma of mean	4.00	2.60	1.40
Standard error of mean difference	—	—	.77
Range	15.0–.24	13.3–.25	

* One case with index of 100 not included.

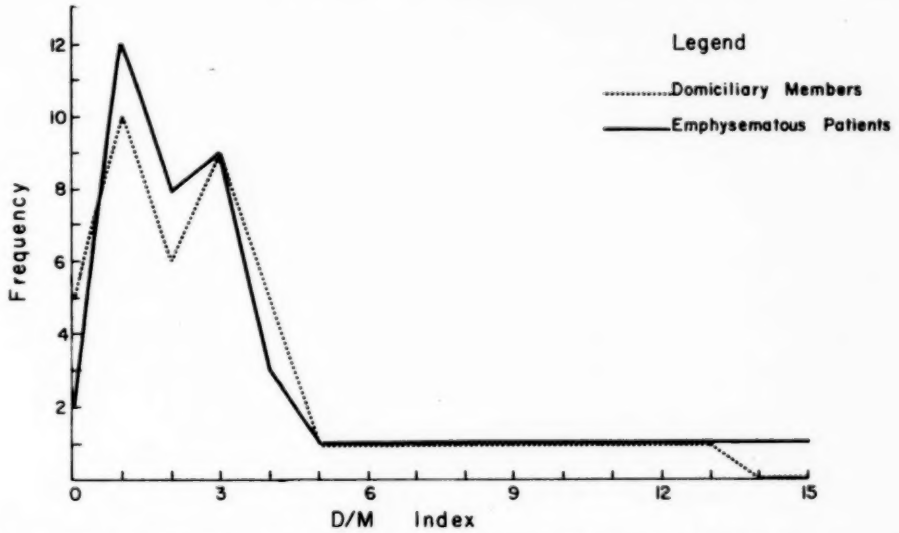

FIG. 1. Dur-Moll indices for the emphysema group (33 members) and the domiciliary control group (43 members).

the Waltisbuehl method of Dur-Moll study, the two groups did not differ beyond the limits of pure chance.

The comparative Dur-Moll indices for the emphysema group and the domiciliary control group are illustrated in Figure 1.

Social indices

According to Szondi (13), the various vectorial constellations of the Szondi profile may be arranged in a social-asocial continuum. He states that the so-called social index for the normal zone lies between 40 and 60 per cent. Criminals, perverted psychopaths, mentally ill, senile, and visually defective subjects (the asocial group) rank under 40 per cent, whereas neurotic subjects, (that is, persons with a stringent superego in the Freudian sense) rank between 60 and 75 per cent.

The social indices were computed for the members of the emphysema and domiciliary control groups. The results are listed in Table 6. It will be seen that the sigmas of the means were so large that the data of the two groups could not be validly compared, unless much larger samples were obtained. Moreover,

TABLE 6

Statistical Comparison of Social Indices

Statistic	*a*. Domiciliary Control Members (N = 43)	*b*. Emphysematous Members (N = 33)	*a* − *b*
Mean	40.5	41.4	−0.9
Median	42.5	39.0	3.5
Mode	42.5	35.0	7.5
Sigma of mean	24.8	21.9	2.9
Standard error of mean difference	—	—	1.69
Range	53–31	50–30	

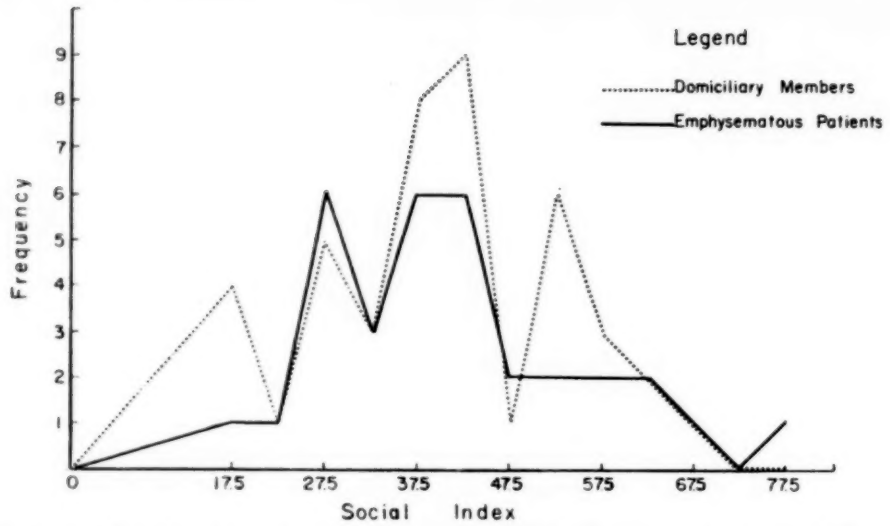

FIG. 2. Social indices for the emphysema group (33 members) and the domiciliary control group (43 members).

the standard error of the mean difference was much too high for statistical significance. Accordingly, it may be concluded that any difference in the social index between the two groups could be due to chance factors. Figure 2 illustrates this comparison of the two groups.

Factorial tendencies

Since the symptomatic reactions, Dur-Moll indices and social indices indicated no significant difference between the emphysema group and the domiciliary control group, we explored the situation with respect to factorial tendencies. Table 7 shows the relative values of the 16 tendencies of the 8 factors comprising the 4 Szondian drives for the emphysema group, the domiciliary control group, and the normal control group. It will be noted that both institutional groups differed widely from the European noninstitutional control group with regard to the various factorial tendencies. To a lesser degree, the emphysema group differed from the domiciliary control group, but the difference in all the factors except "e" and "p" was very significant. These differences will be discussed in detail later.

In Table 8 are listed the x^2 differences among the various factors in the emphysema and domiciliary control groups. In 5 of the 8 factors the differences were at the .01 level of confidence or better.

FACTORIAL ANALYSIS (Tables 7 and 8)

h factor

The h+ tendency[1], which represents sensuous, undifferentiated personal amorousness, was excessively accumulated in both the emphysema (85 per cent)

[1] For a more detailed discussion of Szondian drives, factors and tendencies, see Szondi, L., Moser, U., and Webb, M.: The Szondi Test in Diagnosis, Prognosis and Treatment. Philadelphia, J. B. Lippincott Co., 1959, pp. 19-21 and 35-38.

TABLE 7

Percentages of Szondi Test Factorial Reactions

Reaction	Emphysema Group (N = 33)	Domiciliary Control Group (N = 43)	European Noninstitutional Group (N = 200)
h+	85.0	89.6	67.0
h−	5.2	1.6	9.0
h±	6.4	3.0	13.0
h 0	3.4	6.0	11.0
s+	44.0	62.0	30.0
s−	23.0	16.0	28.0
s±	7.8	6.9	14.0
s 0	25.2	19.2	18.0
e+	23.3	18.4	19.0
e−	31.0	36.3	31.0
e±	9.0	11.6	14.0
e 0	36.7	33.7	38.0
hy+	2.7	7.0	18.0
hy−	77.2	67.0	45.0
hy±	6.7	7.8	13.0
hy 0	13.4	16.2	24.0
k+	4.5	4.0	11.0
k−	70.0	79.0	56.0
k±	8.2	6.5	16.0
k 0	17.3	10.5	17.0
p+	17.5	22.8	10.0
p−	45.3	40.4	66.0
p±	9.7	11.7	8.0
p 0	27.5	24.6	18.0
d+	36.0	23.5	39.0
d−	20.0	33.0	18.0
d±	11.5	6.0	8.0
d 0	32.4	36.7	35.0
m+	40.0	30.9	53.0
m−	30.0	33.0	21.0
m±	10.0	8.0	14.0
m 0	20.0	28.4	22.6

and the domiciliary control (89.6 per cent) groups. This marked predominance of the h+ reaction in both the institutional groups was in contrast to the 67.0 per cent accumulation observed in the normal population group, and was far greater than the theoretically probable 30.7 per cent for + reactions with the Szondi test. These results would seem to indicate an unsatiated or inexorable need for personal amorousness—to be the recipient of love, affection, tenderness

TABLE 8

X^2 Factorial Differences between Emphysema Group (N = 33) and Domiciliary Control Group (N = 43)

Factor	X^2	P
h	39.8	<.001
s	25.0	<.001
e	4.92	<20>10
hy	32.0	<.001
k	7.6	<.05
p	2.5	<50>30
d	30.0	<.001
m	11.1	<.01

and devotion. This phenomenon may be related to the deviant marital pattern previously noted in these two groups.

The h− tendency denotes an ideal, altruistic love for mankind in general. There was a significant difference in this respect between the normal (9.0 per cent) and emphysema (5.2 per cent) groups, but in both cases the tendency was below the 30.7 per cent theoretical frequency for minus reactions in the test. On the other hand, the frequency of this response in the emphysema group (5.2 per cent) was more than three times greater than in the domiciliary control group (1.6 per cent).

The h± reaction, indicating ambivalency between the h+ and h− tendencies, was observed twice as often in the emphysema group as in the domiciliary control group (6.4 versus 3.0 per cent), but only half as often as in the normal group (13.0 per cent). The theoretical probability for the h± reaction is 15.8 per cent.

The h0 or open reaction, indicating that the h factor has been satisfied in a native form or indirectly through sublimation, socialization or reaction formation, was twice as frequent in the domiciliary control group as in the emphysema group (6.0 versus 3.4 per cent) but only half as frequent as in the normal group (11.0 per cent). This indicates a greater inhibition of symptomatic behavior in relation to the h need within the emphysema group. The theoretical probability for the open reaction is 22.6 per cent.

These data relating to factor h indicate that, to a greater extent than the normal population of similar age, both the domiciliary control and emphysema groups exhibited an h+ tendency representing an accumulation of sensuous, undifferentiated individualistic amorousness that remained unsatiated. Both groups manifested an excessive desire for passive amorous activity—to be the passive object of love, affection, tenderness and devotion. This tendency in emphysematous patients is recognized by medical specialists. It represents, moreover, a desideratum which institutional life cannot fulfill, though this observation in no wise implies that the institutional life plays a causative role in the development of this accumulated need. The h+ tendency, in its loaded

form as usually found in the emphysema and domiciliary control groups, represents the amorous factor in a primitive rather than a humanitarian or highly cultured form. There was, however, a significant difference between the emphysema and the domiciliary control groups with respect to the h− tendency, even though the tendency was much below the theoretical average for all groups. The relatively higher level in the emphysema group indicated that its members on the whole possessed more altruism and more tolerance for, and interest in mankind in general. They were, therefore, less primitive in this tendency. Both the emphysema and domiciliary control groups were significantly below the normal group in respect to the frequency of the h± reaction. This reaction of ambivalence is an inhibitive force which operates to restrain the s factor. This indicates that the emphysema group and, even more, the domiciliary control group tended to inhibit aggressive-like reactions far less than did the normal population.

s factor

The s+ tendency was markedly predominant (62.0 per cent) in the domiciliary control group. It was the predominant reaction, however, for all 3 groups. It was not so pronounced for the emphysema group (44 per cent) as the h+ reaction, and in the normal group it barely exceeded the s− reaction (30.0 versus 28.0 per cent). The loaded s+ reaction in the domiciliary control group where it was strongest revealed a tendency toward restless activity and aggressiveness, allayed, however, by the over-compensating h+ reaction. The latter has an amalgamative effect on the s+ tendency and renders the subject psychosexually passive, though tense through the frustration of his psychosexual needs. In contrast, the tendency toward restless activity and aggressiveness was no serious problem for members of the emphysema group.

The s− tendency, which is the antithesis of the s+ reaction, indicates a striving for feminine passivity, submission and subserviency. It was one-third greater in the emphysema group than in the domiciliary control group (23.0 versus 16.0 per cent), but this unsatiated need was still markedly stronger in the normal population group (28.0 per cent). Thus, normal subjects within the age group represented here tended to manifest passive, effeminate tendencies to a greater degree than did the emphysema group. In the domiciliary control group, however, the s− reaction was relatively less significant. In the latter group the aggressive tendencies predominated over the passive tendencies in a ratio of 4:1, in contrast to a ratio of 2:1 for the emphysema group, and approximately 1:1 for the normal group.

The s± reaction, which represents an ambivalence between the aggressive masculine and the passive feminine tendencies and which acts as a restraining influence on the accumulated h+ tendencies, occurred in approximately equal proportions between the domiciliary controls and the emphysema groups (7.8 versus 6.9 per cent), but occurred approximately twice as frequently in the normal group (14.0 per cent). These percentages show the relatively impotent inhibitive tendencies of the emphysematous patients in the psychosexual vector.

The s0 or open s reaction, which denotes an absence of accumulated aggressive or passive tendencies (that is, an acting out of these strivings), was present in approximately the same proportions of the emphysema group (25.2 per cent), the domiciliary control group (19.2 per cent) and the normal group (18.0 per cent).

When the s factor was considered as a whole, both the emphysema and domiciliary control groups manifested a predominance of the s+ or aggressive factor in relation to the s− or passive factor. In the normal group, however, the tendencies were about equally divided. The predominance of the aggressive factor was considerably more pronounced in the domiciliary control group than in the emphysema group.

e factor

The e+ reactions (Table 7) were below the theoretically expected 22.7 per cent for both the domiciliary control and normal groups (18.4 versus 19.0 per cent), but were above the expected level for the emphysema group (23.3 per cent). This tendency, which represents the ethical component of the personality, or element of conscience (that is, the urge to make amends and to be conscientious and scrupulous), was more potent in the emphysema group, though not to a statistically significant degree.

The antithetic e− tendency, which indicates not only the absence of ethical standards, but also a proclivity to accumulate the gross effects of rage, anger, vengeance, hatred, jealousy and envy was, on the other hand, appreciably weaker in the emphysema group than in the domiciliary control group (31.0 versus 36.3 per cent), but was equal to that in the normal group (31.0 per cent). In all 3 groups the e− reaction attained a significantly higher frequency than did the e+ reaction.

The e± reaction, which represents an ambivalence between ethical principles on the one hand and base tendencies on the other, was lowest in the emphysema group (9.0 per cent), contrasted with 11.6 per cent for the domiciliary control group and 14.0 per cent for the normal group. This was in accord with expectations, since the emphysema group appeared to have strivings toward ethical goodness to a greater degree than the other two groups.

The e0 (open reaction) occurred with approximately equal frequency in all 3 groups and was the predominant e type. This would denote a release or acting out of either ethical or base tendencies to about the same degree in all 3 groups.

When the e factor was considered in the aggregate, the emphysema group was slightly more ethical than the 2 control groups. However, in all 3 groups the traits of potential anger, rage, jealousy, vengeance, hatred and envy predominated over the traits of goodness.

hy factor

The hy+ reaction (Table 7), which represents a striving for esteem, recognition, vindication and self-display was infrequently observed in all groups.

However, the frequency was approximately three times as great in the normal population as in the emphysema and domiciliary control groups (normal population 18.0 per cent, domiciliary control group 7.0 per cent and emphysema group 2.7 per cent). This denotes a serious lack of, and need for self-expression in the latter groups, particularly in the emphysematous patients.

The observed frequency of the hy− factor was far above its theoretically expected frequency (30.7 per cent) in the domiciliary control group (67.0 per cent) and slightly above the expected frequency in the normal group (45.0 per cent). It was distinctly below the expected level in the emphysema group (77.2 per cent). Thus the domiciliary control member, and to a still greater extent the emphysematous patient is revealed as a person who strives for self-effacement, self-concealment and withdrawal from social contacts.

The hy± tendency, which represents an ambivalence between self-display and its corollaries on the one hand, and self-concealment and its corollaries on the other, was approximately equal in the emphysema (6.7 per cent) and in the domiciliary control (7.8 per cent) groups, but was almost twice as frequent in the normal group (13.0 per cent). This difference appeared to be due to the fact that the 2 institutional groups, more consistently than the normal group, followed the behavioral pattern typical of the hy− reaction.

The frequency of the open hy reaction was almost twice as low in the emphysema group (13.4 per cent) as in the normal group (24.0 per cent), but only slightly lower than in the domiciliary control group (16.2 per cent). The emphysema and domiciliary control groups, accordingly, were less likely to live out their needs for self-concealment and self-effacement; hence, their need for withdrawal from the world for the most part was frustrated. That this tendency antedated their institutional life was revealed in a previous study (14).

When the hy reactions were considered as a whole, it was clear that both the emphysema and domiciliary control groups differed significantly from the normal group, in that the first two were strongly oriented toward self-effacement and self-concealment. As indicated in Table 8, there was a statistically significant difference between the emphysema and domiciliary control groups with regard to the hy− trait, the emphysema group predominating in their accumulation of this unsatiated need.

k factor

The k+ factor (Table 7) was an infrequent reaction in all 3 groups—domiciliary control 4.0 per cent, emphysema 4.5 per cent, and normal 11.0 per cent. This reaction, which depicts a masculine ego ideal, an internalization of objective ideals and a contraction of psychic interests and contacts, was approximately equal in the emphysema and domiciliary control groups, but well below the level of that in the normal group. The distinctly low k+ percentages in both institutional groups was indicative of the lack of a masculine ego ideal in these patients and was consonant with their passive, effeminate characteristics.

The k− reaction predominated in all 3 groups, but was much higher in the domiciliary control (79.0 per cent) than in the normal (56.0 per cent) group;

it was intermediate in the emphysema group. This reaction denotes a tendency toward renunciation or depreciation of worldly values, sometimes to the point of self-sabotage, and a predisposition toward inhibition and repression. The typical defensive mechanism represented by this reaction is repression—a classic neurotic mechanism. This tendency is often seen in cases of addiction. In this study, it was present in highest degree in the domiciliary control group—a group exhibiting a relatively large number of neurotic complaints, with all too frequently a history of alcoholism. To a lesser extent, such tendencies also characterized the emphysematous group.

The k± reaction denotes both a masculine ego ideal and an ambivalence between the tendency to internalize and encapsulate conflicts within the psyche on the one hand and to repress them and prevent their intrusion into conscious awareness on the other. It was observed more often in the emphysema group (8.2 per cent) than in the domiciliary control group (6.5 per cent). This ambiguous tendency, however, occurred twice as often in the normal group (16.0 per cent). It is precisely this ability to attain an ambivalent state between two opposing tendencies which enables the normal subjects to lessen the accumulation of k− tension. Since the k± represents also a masculine ego ideal, the higher frequency of this reaction in the normal group emphasizes the relative lack of adequate masculine ideals in the domiciliary control and emphysema groups.

The open k (k0) reaction indicates that the ego (the internal censorial system of the personality) momentarily is not functioning; it also represents an ego with feminine ideals. It was almost twice as frequent in the emphysema group (17.3 per cent) as in the domiciliary control group (10.5 per cent). In the normal group it alternated equally with the k± reaction (17.0 and 16.0 per cent, respectively). Thus members of the emphysema group were more prone to the sudden development of an impotent ego or censorial system (typical of the paroxysmal disorders) than were members of the domiciliary control group. Moreover, the emphysema group exhibited feminine ego ideals more frequently than did the domiciliary control group.

When the k factorial reactions were considered in the aggregate, it appeared that the k− reaction was relatively most frequent in the domiciliary control group, the k+ reaction in the normal group, and the open k reaction in the emphysema group. Hence, the tendency toward addictive practices, toward self-sabotage, and the disparagement of worldly values was strongest in the domiciliary control group and next strongest in the emphysema group. The latter group exhibited the weakest ego control pattern and was the most effeminate in its ego ideals. There was a significant difference (Table 8) between the domiciliary control and emphysematous groups with regard to the k factor.

p factor

The p+ reaction (Table 7) typifies feminine ego ideals, a tendency toward grandiose thinking, and an obsession of the psyche with antitheses whose incongruities are not recognized. It was only about half as frequent in the normal

(10.0 per cent) group as in the domiciliary control (22.8 per cent) and emphysema (17.5 per cent) groups. Accordingly, the normal group was more realistic in its mental processes and the domiciliary control group was the least realistic. The latter was also the most grandiose.

The p− reaction denotes the tendency to project, to externalize problems, and to displace them extrapsychically. This tendency was a third greater in the normal group than in the others (66.0 per cent in the normal group contrasted with 40.4 per cent in the domiciliary controls, and 45.3 per cent in the emphysema group). The normal group tended to rationalize and to externalize problems, whereas the 2 institutional groups displayed much less tendency to utilize this mechanism.

The p± reaction, which is feminine in type and indicates ambivalence between inflative and projective tendencies, was about equal in frequency in the domiciliary (11.7 per cent) and emphysema (9.7 per cent) groups, but was somewhat less (8.0 per cent) in the normal group. This was to be expected, since the normal subjects were more masculine in their ideals.

The p open (p0) reaction, which is masculine, was not markedly different in frequency among the 3 groups. Curiously enough it was highest in the emphysema group, in which feminine ego ideals were also highest. There was no statistically significant difference between the domiciliary control and emphysema groups with respect to the p factor.

When the p factor was considered in the aggregate, it appeared that the domiciliary control and emphysema groups were more feminine in their ego ideals than were the normal subjects, and that they tended to repress their conflicts to a greater extent and were less inclined to project them on the outside world.

d factor

The d+ tendency (Table 7), indicates the desire to seek and acquire new amorous objects, to seek change, to seek a different environment, to become mobile and to be variable. It was strongest in the normal and emphysema groups (39.0 and 36.0 per cent respectively). The tendency was a third stronger in the emphysema group (36.0 per cent) than in the domiciliary control group (23.5 per cent). This would denote more of a tendency toward restlessness, more variability in the choice of love objects, and less tolerance for routine situations in the emphysema group than in the domiciliary control group.

The antithetic d− reaction represents the tendency toward constancy and loyalty to a love object or a surrogate thereof. It was observed almost twice as frequently in the domiciliary control group (33.0 per cent) as in the normal group (18.0 per cent), with the emphysema group falling about midway between (20.0 per cent). Thus the normal subject was more variable, more persistent in his search for new love objects of a personal or material nature, and less inclined to maintain a steadfast loyalty to such objects. The member of the domiciliary control group was the converse; he remained loyal to the amorous object, which may even have been the institution itself. The members of the

emphysema group ranked midway between the other two. Thus, although the emphysematous group tended to be variable in relation to love objects, the domiciliary group tended to be more constant.

The d± reaction, depicting ambivalence in amorous and social relationships, was markedly greater in the emphysematous group (11.5 per cent) than in the domiciliary control (6.0 per cent) or normal (8.0 per cent) groups.

The open d reaction indicates a living-out of the objective relationship to amorous objects of a personal or material nature on a casual basis. There was no significant difference among the 3 groups (normal 35.0 per cent, domiciliary control 36.7 per cent, emphysema 32.4 per cent).

When the d reaction was considered as a whole, the tendency toward variability, inconstancy and seeking after new love objects and experiences predominated in the emphysema and normal groups, whereas the tendency toward loyalty and stability of attachment to an amorous object of a personal or material nature prevailed in the domiciliary control group. Members of the latter group seemed constant in their loyalty to the institution, whereas the members of the emphysema and normal groups showed much less tendency to remain steadfast and loyal to one love object or ideal. The 3 groups differed little in their tendency to inhibit or to live out their respective tendencies in relation to the amorous ideal, whatever its nature. There was a very significant statistical difference in the d need between the emphysema and domiciliary control groups.

m factor

The m+ tendency (Table 7), which relates to orality and the tendency to cling tenaciously to a love object, ranked highest in the normal group (53.0 per cent) and lowest in the domiciliary control group (30.9 per cent), with the emphysema group falling between (40.0 per cent). This indicated that the normal group adhered more tenaciously to its amorous objects, whereas the domiciliary control group was less steadfast in this respect.

The m− reaction represents a tendency toward detachment from amorous affiliations and emotional involvement in interpersonal relations of every type. As expected, it occurred more frequently in the domiciliary control group (33.0 per cent), perhaps because their attachment was to an impersonal institution and hence frustrating with regard to amorous needs. Steadfastness of attachment to amorous objects was highest in the normal group and, conversely, instability toward amorous objects was least pronounced (21.0 per cent). The emphysema group was more unstable in its attachment to love objects than was the normal group, but not as much so as the domiciliary control group.

The m± reaction, representing ambivalence in interpersonal attachments with a tendency both to strive for and to avoid such relationships, was almost twice as common in the normal (14.0 per cent) as in the domiciliary control (8.0 per cent) group, with the emphysema group again falling between.

The open m (m0) reaction, representing casualness, spontaneity, super-

ficiality and inconstancy in interpersonal attachments, was highest in the domiciliary group (28.4 per cent), owing perhaps to the impersonal attachment to the institution. The percentages were approximately the same for the emphysema and normal groups.

When the m factor was considered in the aggregate, it appeared that the member of the emphysema group was much more dependent, possessed significantly more orality and was more tenacious in his attachment than was the typical member of the domiciliary control group. The member of the normal group, however, was even more tenacious in his attachment, which is a contradiction of the oft repeated assertion that the asthmatic (and by implication perhaps the emphysematous patient) is an excessively dependent, oral, clinging type of person. Conversely, the domiciliary control member was less dependent upon personal attachments than the emphysema group member, whereas the normal subject showed a greater tendency to maintain personal attachments once they were made and a greater reluctance to sever such bonds. The domiciliary control group, then, was the most unstable, and the emphysema groups was the next most unstable in the area of interpersonal attachments. The difference in this regard between the emphysema and domiciliary control groups was at a very significant level of confidence.

VECTORIAL ANALYSIS (Tables 9–12)

S(psychosexual) vector

The prevalent S vectorial patterns for the 3 groups are shown in Table 9. The configuration for the normal group of similar age was S = h+, s+, −, which is masculine but which approaches an effeminate passive pattern. For the younger and middle-aged male group of the normal population it is S = h+, s+. In the domiciliary control group the pattern was S = h+ !!, s+, which denotes an accumulation of tension in the h+ tendency to a slightly greater degree than in the emphysema group, as well as tension in the s factor. The S = h+!, s+ pattern found for the emphysema group is often associated with psychosexual disorders, such as paranoid schizophrenia and sexual deviancies. The configuration for the emphysema group revealed abnormal tendencies within the psychosexual sphere; it was therefore construed as a spurious passivity which was, in reality, an overcompensation for aggressiveness.

TABLE 9

S Vectorial Patterns

Group	S		Type
	h	s	
Normal	+	+	Normal amalgamation
Domiciliary control	+!!	+!	Aggressive pattern with excessive loading in both h and s factors
Emphysema	+!	+	Aggressive pattern with h+ loading

TABLE 10

Prevalent Patterns in the P Vector

Group	P		Type
	e	hy	
Normal	—	—	Normal anxiety
Domiciliary control	—	—!	Hypersensitivity, self-concealment
Emphysema	0	—!	Self-effacement, self-concealment, hypersensitivity

P (paroxysmal or affective) vector

The prevalent patterns in the P vector for the 3 groups are shown in Table 10. The pattern for the normal group indicated only a moderate degree of anxiety. In contrast, for both the domiciliary control and emphysema groups there was an exaggerated tendency toward hypersensitivity and self-concealment, as well as a tendency toward the development of delusions of prejudice and reference and a tendency toward hallucinations. This perhaps explains why some emphysematous and asthmatic patients tend to become psychotic, either with or without the administration of corticotropin (ACTH). As a matter of fact, in some patients of the emphysema group the Szondi profiles were indicative of an epileptiform paranoid disorder, in some instances corroborated by the anamnesis. The fact that both the emphysema and domiciliary control groups were institutionalized populations would not seem to be a significant factor.

Sch (ego) vector

The prevailing patterns in the Sch vector for the 3 groups are shown in Table 11. The emphysema and domiciliary groups were characterized by an encapsulative, repressive type of ego, whereas the normal group was characterized more by a projective, externalizing type of ego. The domiciliary control, and to an only slightly lesser extent the emphysematous patient, tended to depreciate worldly values, to disparage self and to exhibit addictive or self-destructive tendencies. A member of these 2 groups internalized rather than projected his conflicts on the outside world. He was more likely to somatize his conflicts

TABLE 11

Sch Vectorial Patterns

Group	Sch		Type
	k	p	
Normal	—	—!	The projective ego
Domiciliary control	—!!	—	The encapsulative, self-sabotaging, depreciative ego
Emphysema	—!	—	The encapsulative, self-sabotaging, depreciative ego

TABLE 12
C Vectorial Patterns

Group	C		Type
	d	m	
Normal	0	+	Firm emotional bond
Domiciliary control	0	±	Ambivalent emotional bond
Emphysema	+	+	Unstable, fickle, emotional bond

than to resolve them through accommodation to the exigencies of the environment.

C (contactual) vector

The predominant vectorial patterns in the C vector for the 3 groups are shown in Table 12. Members of the normal group in the 61–70 year age category were inclined to cling steadfastly to love objects and to place a high value on interpersonal relationships. The domiciliary control group members were ambivalent in their ties to other persons, and hence were unstable in their interpersonal relationships. The emphysema group members were inclined to be continually making and breaking emotional ties, indicating social and emotional immaturity in this respect.

DISCUSSION

Szondian depth psychology (15) postulates that asthma in both childhood and adulthood is a genetically determined disease belonging to the cognate group which comprises the paroxysmal disorders. These disorders include epilepsy and its lesser manifestations (petit mal, narcolepsy, pyknolepsy, absence, fugue, rage, substuporous states and psychosis epileptica), as well as its equivalents (migraine-vasoneurosis, stuttering-stammering, asthma-eczema, and enuresis), and likewise the monomanias (poriomania, dipsomania, pyromania, kleptomania and thanatomania). The anamneses of asthmatics would appear to confirm this hypothesis, but nowhere does the scientific literature discuss the cognates of primary obstructive pulmonary emphysema. The present study was, therefore, designed to test the Szondian hypothesis with respect to this specific group.

It would have been desirable to utilize a normal control group of American subjects. Unfortunately, however, Szondi test norms are at present available only for significantly large groups of Hungarian and Spanish subjects of comparable age. Nevertheless, the results of the present study indicate that significant differences existed with respect to many important aspects of the personality, between the emphysema and control groups in a United States Veterans Administration domiciliary, and also between these two groups on the one hand, and the noninstitutionalized European normal control group on the other hand.

In particular, the present study confirms the presence of traits in the em-

physema group which previous investigators have noted in the bronchial asthma group, namely, hypersensitivity, marked passivity, effeminateness, emotional immaturity, insecurity, and ambivalence in relationships to amorous subjects and their objective surrogates. In addition, the present study revealed still other traits or conditions, such as a markedly accentuated and unsatiated need to be the object of love, affection, tenderness and devotion, coupled, however, with an undue accumulation of the unsatiated aggressive need arising presumably from the unsatisfied amorous needs mentioned. Furthermore, there was a need for self-effacement and concealment accompanied by a post-paroxysmal feeling of diffidence and even chagrin. There was also a pronounced tendency toward renunciation, which in many cases approached the magnitude of the self-sabotage tendency noted in cases of addiction. Another characteristic was the instability and fickleness of the emotional bonds to amorous objects of a personal or material nature.

The perennial interpretative problem of cause and consequence arises. Granted that our data reveal a significant correlation between the syndrome of primary obstructive pulmonary emphysema on the one hand and certain personality traits on the other, there is still the question of whether this particular constellation of personality traits is a causative factor in emphysema as described, or whether it is a psychologic consequence of the physical disease process itself. Further studies which employ longitudinal differential diagnostic methods will be necessary to determine this point. It is hoped that the present investigation will serve as a paradigm for other studies relating to the psychologic factors inherent in emphysema and other chronic diseases, particularly with respect to their longitudinal aspect. Only depth psychologic studies which take account of the temporal factor in a differential setting can portray a sufficient number of personality facets to render possible a holistic appraisal of the personality. Such an assessment is indispensable for an investigation of the etiologic factors of chronic disease. Studies like the present one may be conducted by means of group statistical procedures, or they may employ the analytic case method. Szondian depth psychology in the study of other disorders has utilized both methods. Were it not for space limitations, the present study might well have used both techniques to analyze the data.

SUMMARY

A group of 33 patients with primary obstructive pulmonary emphysema, residing in a Veterans Administration domiciliary, were compared with a group of 43 nonemphysematous members of the same domiciliary, and in some respects also with a group in the European general population of similar age, with respect to personality traits measured by the Szondi test, a depth psychologic procedure. In each case the test was individually administered 10 times, with at least twenty-four hours intervening between successive tests. The results were as follows:

There was no significant difference between the emphysema and control domiciliary groups with respect to such indicators of martial instability, as

celibacy, separation and divorce. These conditions, however, were twice as frequent as in the normal population.

Eight-five per cent of the emphysematous patients suffered from a paroxysmal disorder of either an epileptoid or epileptiform paranoid nature. Fifty-two per cent had chiefly followed peripatetic occupations.

Test results indicated that the members of the emphysema group did not tend to somatize their symptoms any more than did members of the 2 control groups.

On the basis of data obtained by the factorial and vectorial computational methods applicable to the Szondi test, the emphysema group did not differ significantly from the domiciliary control group in the ratio of masculinity to femininity. Both groups were predominantly more effeminate than the general population on the factorial scale but showed symptomatic masculine preponderance on the vectorial scale. The latter result was due to the masculinizing influence of the accumulated tension in the factors h+, s+, hy−, k−.

In relation to the Waltisbuehl Social Index of the Szondi profiles, the results for both emphysema and domiciliary control groups fell within the mean normal range, though they tended to lie on the lower border.

The nonemphysematous domiciliary control subjects manifested the most accentuated need to be the recipients of love, affection, tenderness and devotion. In the emphysematous patients the need was less marked, but was more intense than in the general population. The emphysematous patients manifested this need least symptomatically (repression), whereas the general population showed it the most symptomatically in daily living.

The emphysematous group exhibited less accumulation of unsatiated aggressive needs than the domiciliary control group, but a higher accumulation of this need than the general population. This may have been due to institutional frustrations in the 2 domiciliary groups, and the greater opportunity for members of the general population to discharge the aggressive needs in a noninstitutionalized society. With regard to the tendency to accumulate and suddenly discharge the gross effects of rage, anger, vengeance, hatred, jealousy and envy, there was no significant difference among the 3 groups; the tendency to release these effects predominated over the tendency to accumulate them.

The tendency toward self-effacement, concealment, diffidence and unobtrusiveness clearly predominated in all 3 groups, but was significantly greatest in the emphysema group (chagrin over paroxysmal episodes) and least in the normal group.

In all 3 groups the tendency toward repression of unpleasant conflicts predominated, but the 2 institutional groups possessed this trait to the point of marked renunciation or even self-sabotage. This tendency, however, was most pronounced in the nonemphysematous control group.

Loss of ego control was not predominant in any of the groups, but was almost twice as likely to occur in the emphysema and general population groups as in the nonemphysematous domiciliary control group, owing to the stronger repressive tendency in the latter, perhaps as a result of institutional discipline.

The projective defensive mechanism, although predominant, was not prominent in the emphysema and domiciliary control groups, but it was a significant factor in the normal population.

The emphysema group and the general population group were similar in their tendency to seek continually for new amorous attachments to persons or their objective surrogates. In contrast, the domiciliary control group was much more constant in their attachments to love objects; in this case the institution may well have been the amorous object. The emphysematous patients exhibited a more fickle, unstable emotional bond to worldly objects, both personal and material, than did the nonemphysematous controls, and the normal subjects displayed the firmest emotional bonds of all.

The differences between the emphysematous patients and the nonemphysematous controls were significant in all the areas tested by the Szondi test except the "e" (ethical) and "p" (projective) tendencies. This was confirmed by chi square data.

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INTEGRATION OF THE GENERAL HOSPITAL AND THE NURSING HOME IN THE TOTAL CARE OF THE AGED AND INFIRM

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The purpose of this article is twofold: first, to demonstrate the desirability of a closer working relationship between the general hospital and the nursing home in the total care of the aged and infirm, and second, to present an approach to the problem of the high cost of medical care.

NEED FOR COORDINATED PROGRAM

The real need for this coordinated program is shown by the increasing number of patients vegetating in convalescent homes, occupying hospital beds or simply on public assistance rolls. There are at present some 50 million Americans who are middle-aged or beyond, and 16 million of these have already passed their sixty-fifth birthday. The number of Americans past the age of 65 will have reached 20 million in ten years. According to one estimate, three-fifths of these will have an annual income of less than $1000 annually. The aged are hospitalized about three times as often as the population in general and three-fifths of persons past the age of 65 are chronically ill. Many of them are forced into idleness, poverty and even illness by the very programs designed to give them social security. Denying social security to those who stay on the job by forcing them to retire from lucrative positions at the age of 65 is unrealistic and comes at a time in their lives when medical services are most needed. This situation may become worse in the future. The aged are now a distinct social unit and a group apart. Their plight has aroused a sleeping public to tremendous activity. Politicians, sociologists, medical economists and others have made innumerable surveys and studies in an attempt to solve this extremely complex problem.

It is now axiomatic that there is no end in sight for the increasing cost of medical care. Medical indigency increases in direct ratio to the rising cost of medical care. This poses an increasingly acute economic problem for the individual, his family and all the responsible public and volunteer agencies.

There can be no compromise with good medical care, since its primary purpose is to restore the patient to a state of maximum efficiency. Therefore, it is essential to find ways and means to halt the ever-increasing cost of total medical care. This can be brought about by a more logical utilization of all medical resources, by careful evaluation of the patient's initial and continuing needs, by matching all available facilities as these needs develop, and by a more coordi-

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nated and harmonious adjustment between the hospital and the nursing home. The alternative to professionally conserved utilization of all medical resources may well be a cost explosion, resulting in a state-controlled program. The medical profession can no longer be indifferent and must take a more active part in this program.

UNINTERRUPTED MEDICAL CARE OF PATIENTS WITH CHRONIC DISEASE

Medical research, wonder drugs, early evaluation of the patient, earlier hospital discharge, home-care programs, as well as the various hospital and medical-care programs have all had a measurable effect in reducing the sky-rocketing cost of medical care. These newer concepts have evolved after careful thought, study and testing.

Treatment for illness within a good hospital consists of a series of correlated, integrated scientific appraisals aimed at diagnosis and curative therapy. The disposition of the patient after the acute stage of his illness must have equally careful evaluation. Continuity of care is a key concept in any program of total care for aged patients with their multiplicity of chronic illnesses. When the aged patient is ready to leave the hospital, care should be continued by means of an extension program. This can be carried out either in the patient's home or in a convalescent nursing home equipped to provide good care and nursing for prolonged periods. As soon as a definitive diagnosis is made in the hospital, the nature of future convalescent medical attention should be outlined. From this point on, it is essential to continue uninterrupted medical supervision for the prevention or amelioration of exacerbations in the chronic disease concerned. This is a key factor in the total-care approach.

BETTER INTEGRATION OF HOSPITALS AND NURSING HOMES

Judicious evaluation of the needs of the patient shortens hospital stays, reduces the cost of illness and releases hospital beds for the use of patients who are acutely ill. However, much can still be done in further reducing the average length of hospital stay by a smoother integration between the hospitals and the modern nursing homes. One has but to walk through the wards of any hospital to realize the great need for increased efficiency in the use of these extremely costly hospital beds.

New hospital beds call for a capital outlay of about $27,000 per bed. The population is growing and aging. Therefore, before untold millions of dollars are spent on new hospital beds to meet these ever-increasing needs, careful thought must be given to the fuller utilization of existing facilities.

A coordinated affiliation between the general hospital and the modern proprietary nursing home has many desirable features. For the patient, it would provide continuity of medical care. This would result in better medical and administrative supervision and would greatly improve the patient's chance of return to community living. It would make possible the earlier and more expeditious transfer from the hospital to the nursing home, thus reducing the cost of hospitalization and providing for possible social service follow-up. In addition,

it would greatly simplify the transfer and re-transfer of patients between the two facilities.

For the hospital, it would allow additional bed facilities without capital outlay, but would provide the patient with continued medical control and follow-up. This is a very important feature in teaching hospitals, especially as an aid to research. It would release the hospital beds occupied by patients with non-acute illnesses and create a more active service. It would also allow the hospital medical and nursing staffs more time for the study and care of the acutely ill, and supply additional essential areas for interne training. This plan would thus furnish a more controlled and related procedure for the transfer of patients, as well as a more attractive service for the visiting and resident staffs.

For the Department of Welfare it would include all the desirable features accorded to such patients, thus making medical supervision more acceptable. Welfare administrative procedures would be more simplified and hospital facilities would be more readily available. Many thousands of budget dollars spent on prolonged hospital-stay reimbursement for welfare clients would be saved. The plan would also furnish an interesting statistical guide regarding the possibilities of nursing-care facilities, and would make hospital ancillary services more available to the patient.

For the voluntary insurance plans, a tightly-knit program of integration between hospital care and nursing-home care would result in less costly hospital-supervised facilities for the care of plan members. It would also decrease costly, unnecessary over-hospitalization, and provide a basis for future policy making with respect to plan members who are convalescent or chronically ill.

For the nursing facility, the plan would emphasize more clearly the purpose of the nursing home in community service and its right to a place on the team for care of the patient. The home would also benefit from expert professional guidance in upgrading its operation, since it would be assured of a constant and direct source of referrals and would have readily available hospital facilities for the patients. In addition, service in nursing homes would become more attractive to nursing personnel.

OUTLINE OF AN OPERATIONAL PLAN

The Hospital

1. The hospital to have representation on the medical board of the nursing-care facility.
2. The medical superintendent of the hospital and the medical director of the nursing facility to consult on the operation of the institution, its policies and problems.
3. The medical and surgical staffs of the hospital to make regular rounds.
4. The hospital to make its ancillary services available to patients transferred to the nursing facility.
5. The social service staff of the hospital to continue its interest in discharged patients during their sojourn in the nursing home.

6. The hospital to develop simple transfer and retransfer plans.
7. The hospital to develop a statistical plan for the project.

The Nursing Facility

1. To be geographically convenient and accessible.
2. To meet all requirements of the code.
3. To be large enough to meet the needs of the hospital affiliate.
4. To allow first claim for beds to the affiliated hospital, and ultimately all claim if the volume of work so indicates.
5. To state, and agree to, mutually acceptable admission policies.
6. To accept a carefully developed hospital supervision plan.
7. To provide space and equipment for special services such as occupational therapy, physiotherapy and recreational therapy.
8. To keep complete records on all patients.

The Welfare Department.

1. To agree to, and help develop, a general plan as it affects public assistance clients.

Blue Cross

1. To participate in the development and operation of the plan as it relates to its membership.
2. To develop a method and plan of reimbursement for transferred plan members.
3. To develop an accreditation plan.

CONCLUSIONS

The integration of hospital and nursing-home facilities for the aged and infirm is essential in the total-care approach to the problem of reducing the high cost of medical care.

The success of this plan is dependent upon the earnest and coordinated efforts of the medical profession, hospitals, nursing homes, welfare departments, volunteer insurance plans and nursing facilities. It is obvious that the medical community should take the lead and the responsibility in solving the high cost of medical care, since failure to accomplish this aim will result in another step toward the socialization of medicine.

Social security provisions and retirement programs should be revised so that the senior citizen will not be forced into unproductive idleness or even poverty at an age when he is most in need of money to share in the cost of his medical care. This plan would restore some of his dignity and would help him to regain his place and purpose in society.

THE PROPRIETARY NURSING HOME—A STATISTICAL EVALUATION*

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In one large and important area of medical care for the aging, there is a dearth of public information, a lack of valid statistical material, confusion as to functions, and many misconceptions and prejudices. The foregoing situation pertains to the proprietary nursing home.

The last published national figures on nursing homes and related institutions were listed in a survey by Solon and Baney for the United States Public Health Service in 1954 (1). It was estimated that there were approximately 25,000 homes rendering care to about 450,000 aged and chronically ill persons. The importance of nursing homes in fulfilling the need in such an ill-defined area can be appreciated by considering that Solon and Baney's survey revealed that 91 per cent of all facilities furnishing skilled nursing care were under proprietary auspices. However, these institutions averaged a mere 18 beds per home.

In response to the need to fill the present serious gap in community health services for the aged and chronically ill, recently there has been an upsurge of interest in proprietary nursing homes. The rapid increase in the aging population has carried with it a painful burden of sick aged and incapacitated persons. The proprietary home, though too often small and inadequate, has assumed the major portion of responsibility for providing nursing care for this group.

There are many more reasons why attention is being focused on nursing homes. In addition to the demand for institutional care caused by the soaring aged population, the need is further augmented by many socio-economic factors. Hospitals are crowded and the pressure for beds is becoming even greater. Nursing homes are one of the answers to this problem. The American family lives with ever greater mobility. One family in five moves every year. An older and sick member would hamper this phenomenal transientness that is an outgrowth of our modern industrial society. Since we live in smaller units, there is no longer any room in most of our homes for such exigencies as a chronically sick parent or relative. Another economic factor lies in the employment of all the other adult members of the family. Often it is less expensive and more convenient to seek institutional care for the aged relative. Premature compulsory retirement without proper preparation seems to hasten the mental and physical breakdown that makes institutionalization a necessity. Furthermore, we live in a culture which emphasizes and admires activity, beauty and achievement. These goals engender elder-discarding attitudes in our younger people.

* Supported by a Grant-in-Aid from Mead Johnson Co., Evansville, Indiana.

† Medical Director.

SOURCE OF MATERIAL

The present study was undertaken in an attempt to clarify an obscure and poorly understood segment of medical care facilities in the United States. The study is unique in nursing home research in that the information was derived from an analysis of consecutive patients from the time of admission to the time of discharge over a four-year period. Furthermore, the author was closely concerned with the conduct of the home. In previous studies the statistics were related to a given day; therefore, length of stay could not be determined, and there were no discharge data (2, 3). Another discrepancy arose because the information was obtained by questionnaire, and thus the medical information reported "often lacked the background of medical records or even medical examination" (2).

Our statistical material was obtained from a study of 612 consecutive patients representing 739 admissions and discharges from a nursing home which at present has a capacity of 150 beds. It provides skilled nursing care, supervision by a medical director, and limited occupational therapy, physical therapy and recreational programs. Because of its design and size, there is successful separation of patients according to mental status.

Sex: Approximately 60 per cent (442) of the patients admitted were female, and 40 per cent (297) were male. This is in good agreement with the ratio of male to female in the 65–80 age group of the general population.

Age: The average age at the time of admission for both sexes was 74.5 years. For males it was 77.5 years, and for females it was 72.9 years. It is noteworthy that the average admission age for all patients is somewhat lower than reported in previous studies (2). This difference might be attributed to the availability of facilities and services pleasing and comfortable enough to attract many persons convalescing from illnesses and operations and others coming for a short stay—all of whom tend to be younger than the average (Fig. 1). It is significant that 15 per cent of all persons admitted were under the age of 65. This observation does not support the generally accepted view that all patients in nursing homes are very old. Another interesting finding is that males are admitted at a later age than females. The fact that men tend to maintain their independence longer or adjust more readily to their disabilities might account for this difference in admission age. The distribution of the ages on admission is illustrated in Figure 1.

DIAGNOSES

Diagnoses were established shortly before or after admission by the patient's attending physician, with very few exceptions. Records were obtained on patients admitted directly from hospitals. It is immediately evident from the length of the table of diagnoses (Table 1) that the modern nursing home must be in a position to render individualized service and have available the services and facilities necessary to care for a wide variety of illnesses. Cardiovascular disease in some aspect was the predominant diagnosis, accounting for approximately 80 per cent of all the admission cases; moreover, in the great

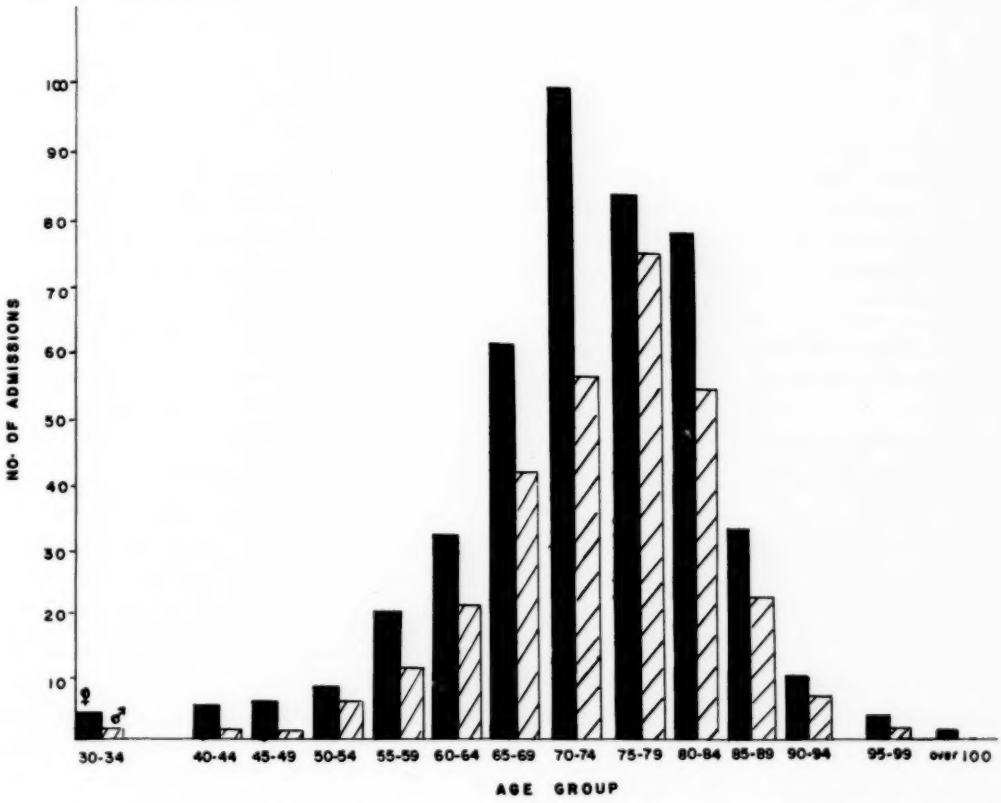

FIG. 1. Distribution of ages at the time of admission. (In Figures 1, 3, 4 and 5, the black olumns represent females and the cross-hatched columns represent males.)

majority of instances there was one or more secondary diagnosis. The multiplicity of diagnoses in the geriatric patient is common knowledge. However, it should be emphasized that multiple diagnoses indicate the need for versatile services and facilities.

In one-third of the cases admitted, one of the diagnoses was senile brain disease. Although this is a fairly large percentage, the real incidence was considerably higher. Apparently many physicians are reluctant to commit themselves in writing, or the family fails to recognize the symptoms or shields the patient. It is difficult for the children to accept the fact that their parent is disoriented and confused; they take great pains to rationalize bizarre behavior and irrelevant thought.

Coronary artery disease was present in a very small percentage of the patients. This might seem unusual; however, many physicians use the term arteriosclerotic cardiovascular disease in an all-inclusive sense, and diseases of the coronary arteries are usually not diagnosed as distinct entities at the time of admission.

Relatively few patients were admitted with a diagnosis of terminal cancer. Apparently the families, because of the finality of the disease and its emotional

TABLE 1
Diagnoses

Disease	No. Patients	% Total Admissions
Cardiovascular disease:		
Arterioscl. heart dis.	321	43.5
Coronary artery dis.	42	5.7
Chronic cong. heart failure	69	9.3
Hypertension	153	23.3
Hemiplegia	128	17.3
Periph. vasc. dis.	14	1.9
Other heart ailments	4	0.5
Senile brain disease	246	33.1
Diabetes	93	12.6
Postoperative convalescence	59	8.0
Fractures: hip/femur	43	5.8
Other fractures	19	2.5
Neoplasms	43	5.8
Parkinson's disease	41	5.5
Chronic prostatic hypertrophy	34	4.6
Arthritis	32	4.3
Other bone diseases	13	1.7
Amputations	29	3.9
Blindness	27	3.6
Pulmonary diseases:		
Asthma	13	1.7
Chronic emphysema	3	0.4
Other	8	1.1
Gastro-intestinal disorders	26	3.4
Psychoneuroses	14	1.9
Trauma (accidents, excluding fractures)	10	1.3
Blood dyscrasias	9	1.2
Urologic diseases	7	0.9
Chronic malnutrition	7	0.9
Obesity	5	0.7
Multiple sclerosis	4	0.5
Epilepsy	2	0.3
Dermatologic disorders	2	0.3
Gynecologic diseases	1	0.1
Pregnancy	1	0.1
Misc. neurologic disorders	13	1.7
Diabetes insipidus	2	0.3
No diagnosis	3	0.4

Total No. admissions: 739 *Total No. diagnoses: 1,541*

implications, assumed the responsibilities and endured the hardships of caring for the patient at home. These patients probably were returned to the hospital during the last days of their illnesses when it was no longer practical for the family to cope with the problem.

Fifty-nine (8 per cent) of the 739 admissions were accounted for by post-

operative convalescent patients (Fig. 2), exclusive of those who had undergone surgery for fractured hip. Postoperative convalescent patients comprised the third largest group; they were considerably younger (average age, 68 years) and their average stay in the home was much shorter than the average for all patients admitted. The availability of facilities for such cases is especially important in helping to relieve the pressure for hospital beds by making earlier discharge possible. The necessity for attractive surroundings for this group is a serious consideration.

The value and necessity of restorative services has been repeatedly emphasized elsewhere. Cases of hemiplegia, fractured hip, other fractures, and Parkinson's disease accounted for 150 admissions, or over 20 per cent of the total. Even with a limited program, much can be done to facilitate earlier discharge from the nursing home.

One unmarried woman, aged 33, was admitted because of uncomplicated pregnancy, to await the end of term. This was a unique situation. At the appropriate time she was transferred to a hospital for delivery.

In 3 cases, no diagnosis was entered on the record. Two of these patients were admitted for short periods while their families were on vacation. About 10 per cent of all admissions were for the purpose of boarding while the responsible caretakers were on vacation or had other temporary obligations which made it necessary to send the patient to an institution. Often, the family just needed a vacation from the patient. Since all of these patients required supervision, they usually were admitted as cases with a specific diagnosis and thus were not listed as a separate category. The third patient admitted without diagnosis was a woman, aged 35, who accompanied her husband. He was convalescing from cardiac surgery. They were from South America, and unfamiliarity with the

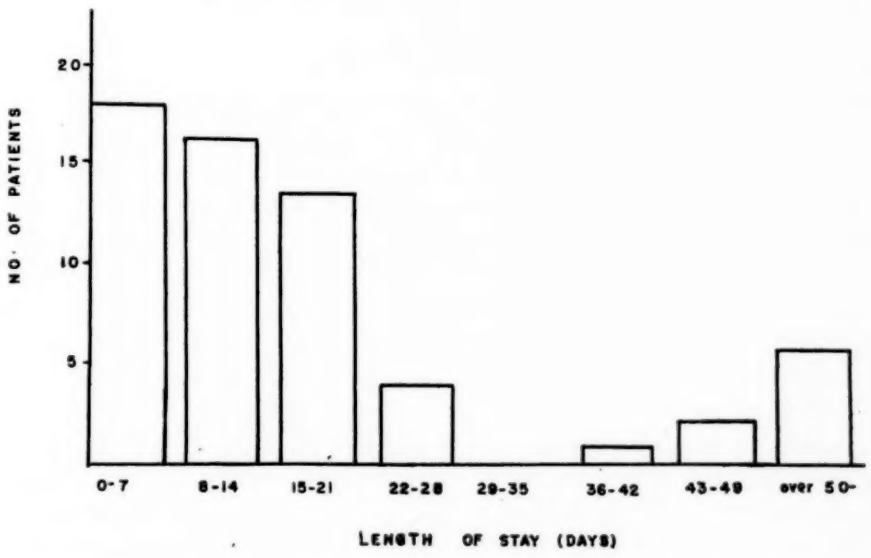

FIG. 2. Length of stay of postoperative convalescent patients

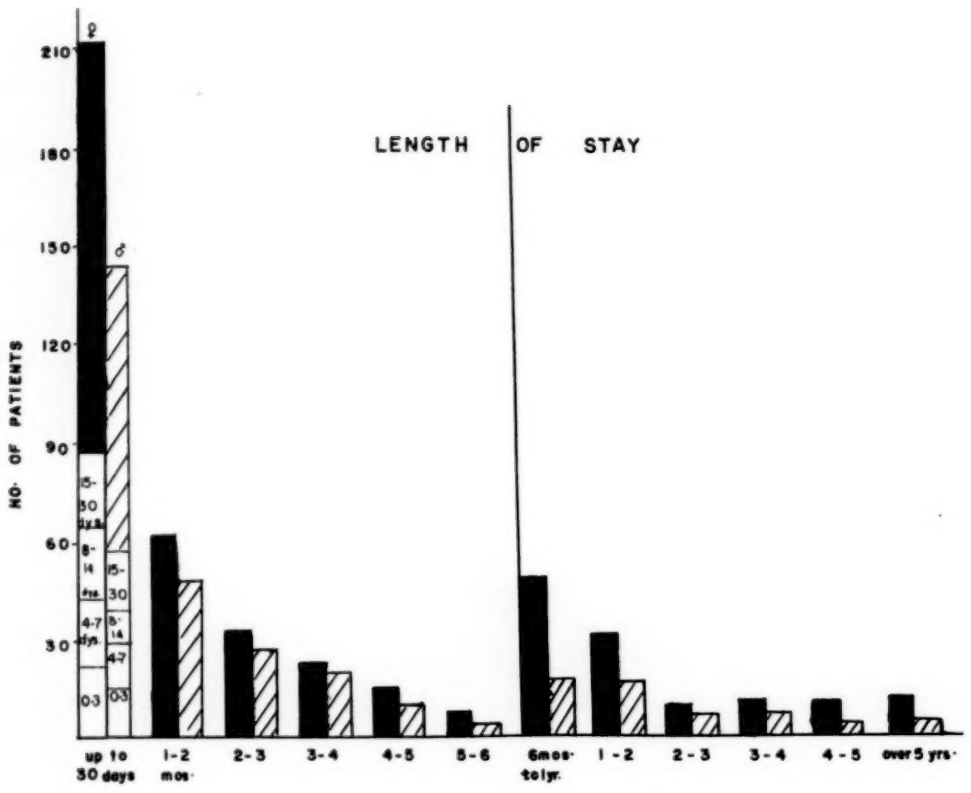

FIG. 3. Length of stay—all patients

community and the language was a contributing factor to her desire to be with her husband.

LENGTH OF STAY

One of the popular misconceptions about nursing homes is the idea that the patient who enters is beginning a long and tedious stay terminating in death. This is not the correct picture for a modern facility, as strikingly illustrated in Figure 3. The most surprising feature was that 358 (more than 48 per cent) of the 739 admitted patients remained in the nursing home less than thirty-one days. The postoperative convalescent patients contributed greatly to this short-stay group; their average length of stay was only twenty-three days (Fig. 2).

The over-all length of stay for females was 210.2 days, and for males 139.2 days. The combined average for the 739 admissions was 181.6 days. This wide variation should be anticipated in any modern nursing institution which provides services and facilities for such a diversity of acute and chronic diseases.

In only 81 cases (11 per cent) did the patient stay for over one year. This hardly compares with the data in Roberts' Maryland study (3), which showed that, on a given day, 50 per cent of the patients in proprietary nursing homes had already been in the institution for one year. Until additional surveys are made

correlating length of stay with type of institution, it is difficult to explain the foregoing differences.

DISCHARGES

An analysis of discharges is presented in Table 2. The majority of the patients were discharged to the care of the family. Of the 83 discharged to a hospital, 36 were eventually readmitted to the nursing home. Only 27 per cent of all those admitted died in the home. Table 2 illustrates the point that the modern nursing home is an institution where patients do not come exclusively "to live," nor exclusively "to die." It was not possible in this study to determine the ultimate fate of the patients discharged to the care of their families, or of the 47 patients who were discharged to a hospital and did not return.

TABLE 2

Distribution of Discharges

Types of Discharge (739 admissions)	Number	% Total Discharges
Home (to family)	395	53.5
By death (in nursing home)	199	27.0
To hospital	83	11.2
To other nursing homes	29	3.9
To non-profit chronic disease home	9	1.2
To non-profit home for aged	11	1.5
To boarding or retirement home	6	0.8
To mental hospital	7	0.9

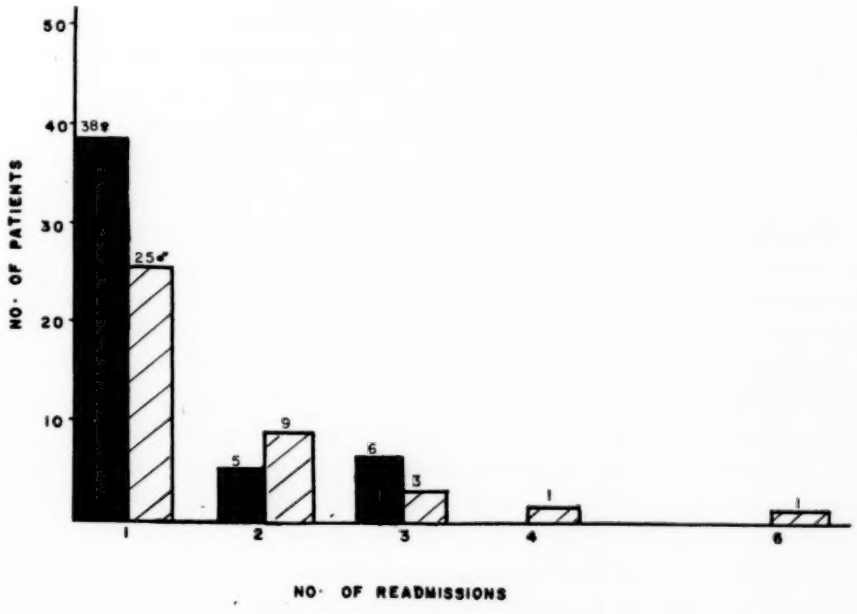

FIG. 4. Number of readmissions

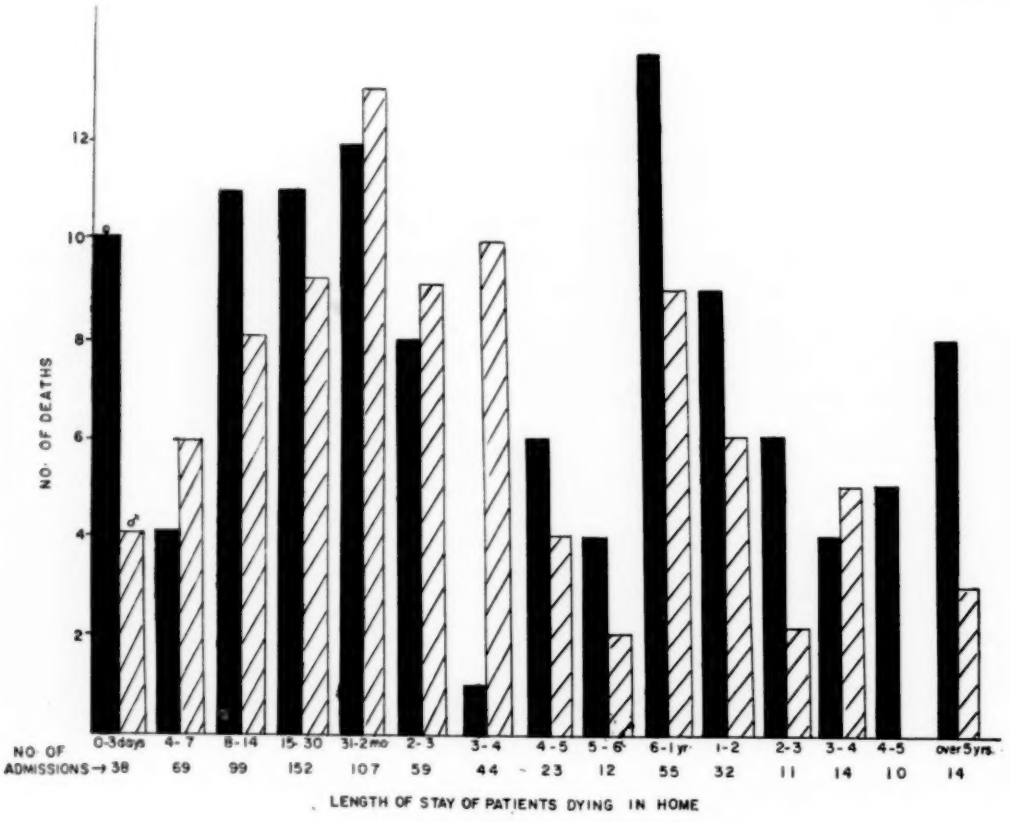

FIG. 5. Distribution of deaths according to length of stay

A small group of 31 patients underwent such short-term hospitalization that they were not considered as discharges. Their beds were reserved for them, they were carried on the census of the home, and all returned.

RE-ADMISSIONS

A significant number of patients were admitted more than once (Fig. 4). Eighty-eight patients accounted for 128 re-admissions in relation to a total of 216 admissions. The maximal number was for a 76-year-old male who was re-admitted 6 more times after his original entry. He had arteriosclerotic cardiovascular disease, moderately severe diabetes, was almost completely blind and had undergone bilateral mid-thigh amputations. He lived in an apartment and every year for seven consecutive years he was admitted for sixteen to twenty days in order to allow his housekeeper to go on vacation. In lieu of a qualified nursing home, the only other facility available to such a patient would be a hospital. This example is given in order to illustrate another unique function of a nursing home. Nonprofit chronic disease institutions are usually not geared for this type of short-term admission, because of waiting lists and the policies of admission committees.

DEATHS

Only 199 patients (27 per cent), in relation to the 739 admissions, died in the home. This supports the contention that the modern nursing home is not an institution where patients come to die. Furthermore, it cannot be said that many patients are discharged to hospitals to die; only 83 (11.2 per cent) were discharged to a hospital and of these 36 were re-admitted.

Figure 5 shows the distribution of deaths correlated with the length of stay in the home. The outstanding fact is that the number of deaths did not vary proportionately with the length of stay. For example, more than one-third of the patients in the 0–3 day group died within this period (14 deaths in relation to 38 admissions), whereas only one-fourth of the patients in the 3–4 month group died within this period (11 deaths in relation to 44 admissions)

COMMENT

On the basis of the evidence presented we attempted to define the role and contributions of the modern proprietary nursing home as a functional medical care resource. What is the picture that emerges? It has been demonstrated that the modern facility should provide the following services:

1. It should render skilled nursing and medical care to any patient not in need of intensive hospital services, regardless of age or sex.
2. It should have facilities for the proper treatment and care of a great variety of acute, chronic and terminal diseases.
3. It should employ the concept of specialization of care, *e.g.*, segregation of the convalescent patients from those suffering from senile brain disease.
4. It should relieve the pressure for hospital beds and thereby promote more efficient utilization of this most valuable resource:
   (a) By promotion of free interchange between hospital and nursing home, by facilitating rapid admission of patients who no longer require intensive hospital care but who cannot go home for one reason or another.
   (b) By providing facilities for the terminal patient who can no longer benefit from hospitalization.
   (c) By continuing a modified program of restorative services for patients who can no longer benefit from intensive rehabilitation.
   (d) By furnishing cheerful, pleasant surroundings for the short-term convalescent patient.
5. It should provide facilities for the seriously disabled or chronic invalid requiring short-term admission while the family has other responsibilities, goes on vacation, or needs a "breather" from the patient. This function has important social and psychologic implications for the relatives as well as the patient.
6. It should be geared for rapid or emergency admissions. This is usually not feasible in similar nonprofit voluntary agencies because of waiting lists, admission committee policies and other pre-admission formalities. This function is especially important to a family suddenly finding itself responsible for a

patient with senile brain disease and discovering that the doors of all available public agencies are closed owing to legal and technical requirements or simply to being overcrowded.

7. It should encourage the return of the patient to the community by the utilization of every medical, nursing and restorative skill available.

8. It should not be a place where unfortunates go exclusively to "live" out the remaining years of their existence, nor a place where the old are sent exclusively to die.

9. It should be attractive, bright and cheerful, in both building and grounds, in order to neutralize some of the overwhelming feelings of guilt suffered by many of the patients' relatives.

We are in the midst of a "population explosion." The over-65 group is increasing with far greater rapidity than any other. There are now about 15,000,000 persons 65 years of age and over in the United States, and it is estimated that by 1980 there will be 30,000,000. This age group carries with it a large burden of chronically ill and incapacitated persons. This emphasizes the need for institutions with high standards. The major response to such a need has been, and continues to be, the proprietary nursing home.

A coordinated, integrated and standardized program for the aged is essential. The modern nursing home, by virtue of the number of aged and chronically ill for whom it now provides services, must be included in any over-all community plan with all other medical care facilities. It must have the stature to accept this responsibility. Problems will still arise. An immediate one, for example, is—How are proprietary homes to be related to nonprofit community resources?

Another aspect should be stressed. To the extent that lay and professional groups clamor for public agencies to construct huge, impersonal and expensive institutional facilities, there will be greatly increased demands for additional tax funds and voluntary contributions. Private enterprise, utilizing modern business techniques and skills and subjected to the stimulus of competition, should be able to provide many of the institutional needs of the sick and the aged with far greater humanity and efficiency, and at much less cost to the taxpayer.

Many additional studies are needed with reference to other facets of management. Such studies should help to correct misconceptions, to confirm the proper functions, and to evaluate the real and potential contributions of proprietary nursing homes.

SUMMARY

An analysis is presented of data obtained from 739 consecutive admissions to a proprietary nursing home over a four-year period.

Although cardiovascular disease and senile brain disease were present in the majority of patients admitted, a wide variety of conditions was represented. The nursing home should provide facilities for the short-term, convalescent patient and restorative services aimed at an early return of the patient to active life in the community.

The significance of the findings relative to the function of the nursing home as a vital medical care facility is discussed.

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Abstracts of Current Literature

THE TREATMENT OF MYCOSIS FUNGOIDES WITH A NEW AGENT, CYCLOPHOSPHAMIDE (CYTOXAN).

Abele, D. C., and Dobson, R. L. *A.M.A. Arch. Dermatol.* **82:** 725 (Nov.) 1960.

Cyclophosphamide (Cytoxan), a potent cytotoxic agent, produced satisfactory remissions in 4 patients with mycosis fungoides in the premycotic or infiltrative stage of the disease. Treatment with 200 mg. daily for fourteen to twenty-one days brought relief of symptoms, clearing of exfoliation, and thinning of infiltrated plaques within ten to fourteen days. Subjective symptoms usually subsided in four to seven days. The only side-effect was moderate alopecia. After the initial treatment period, the dosage was changed to a single weekly dose of 400 to 700 mg., since more prolonged dosage resulted in more severe alopecia. This amount sometimes had to be given in two doses because of the occurrence of nausea with the higher amount—a scheme which on occasion resulted in less satisfactory control of the disease. No hematologic abnormalities were observed, but these should be watched for, since the drug in amounts of 7.5 mg. per Kg. per day (twice the dosage administered) will produce leukopenia. Cytoxan has not as yet been used in the tumor stage of mycosis fungoides. The results reported in treatment of the premycotic lesion justify further trials of the agent.

DERMATOMYOSITIS AND MALIGNANT NEOPLASMS IN ADULTS.

Arundell, F. D.; Wilkinson, R. D., and Haserick, J. R. *A.M.A. Arch. Dermat.* **82:** 772 (Nov.) 1960.

The presence of a silent neoplasm must be suspected in adults with dermatomyositis. A review of cases, excluding dermatomyositis in children, shows the incidence to be approximately 52 per cent, which is higher than generally believed. Among 35 cases reviewed in a twenty-year period, there were no neoplasms in the 12 patients under 40 years of age. Of the 23 patients above 40 years of age, 12 had some type of malignancy. There were 3 males and 9 females. The onset of dermatomyositis preceded diagnosis of the malignancy by an average of six months in 10 cases, by six months in 1 patient, and by two years in 1 patient. In the latter 2, dermatomyositis appeared at the time of progression of the neoplasm. In 6 of 9 patients there was improvement in the dermatomyositis after treatment of the neoplasm. In 3, exacerbation of dermatomyositis occurred when the neoplasm progressed after initial treatment. In 1 case there was an exacerbation of dermatomyositis without extension of the neoplastic lesion. Five of the patients with the combined diseases died. The deaths occurred in patients whose malignant lesions were not treated or whose dermatomyositis did not improve after treatment of the neoplasm.

UMBILICAL HERNIA SECONDARY TO CIRRHOSIS OF THE LIVER. COMPLICATIONS OF SURGICAL CORRECTION.

Baron, H. C. *New England J. Med.* **263:** 824 (Oct. 27) 1960.

It is not generally recognized that the frequency of hernia is increased in patients with cirrhosis of the liver. Analysis of large series of patients with cirrhosis shows that umbilical hernia occurs with greater frequency than in the usual hospital population. In a group of 16 patients with cirrhosis who underwent various technics for the treatment of umbilical hernia, 5 deaths could be attributed to surgery—a mortality of 31 per cent. These patients died from hematemesis and exsanguinating hemorrhage from a ruptured esophageal varix.

In a control series of patients with umbilical herniorrhaphies but no cirrhosis, the postoperative death rate was 3.7 per cent. These cases indicate that a critical hepatofugal collateral circulation exists in the umbilical area. Its development in a vulnerable site and its disruption during the course of umbilical surgery may place a critical load upon the esophageal plexus of veins.

Therefore, an important consideration in surgical correction of defects in the umbilical area in patients with hepatic cirrhosis and portal hypertension is a recognition of the dangers inherent in reducing the capacity of the collateral venous bed. The least disruptive surgical procedure must be performed in order to protect the portosystemic collateral circulation and thus avoid the often fatal complication of hematemesis.

INTRA-ARTICULAR INJECTIONS FOR OSTEOARTHRITIS.

Bonner, C. D. *Rheumatism* **16:** 84 (Oct.) 1960.

Multiple intra-articular injections of hydrocortisone acetate or of prednisolone tertiary butyl acetate at short intervals were given, respectively, to 31 osteoarthritic patients with 56 painful joints and to 16 patients with 25 painful joints. Excellent results were obtained in 84 per cent of the first group and in 92 per cent of the second. Remissions lasted for more than two months in 75 per cent of the hydrocortisone group and in 73 per cent of the prednisolone group. These responses and the length of remission were considerably better than those seen in series of cases reported in the literature wherein a few, or single injections were used. No serious complications occurred. The incidence of such reactions among 50,737 injections reported in the literature in a five-year period is less than 0.02 per cent. Therefore, intra-articular injection with a sterile technic appears to be a safe procedure.

THYROTOXICOSIS IN ELDERLY PEOPLE.

Browning, R. W. *J. Arkansas M. Soc.* **57:** 195 (Oct.) 1960.

Elderly persons may have the classic or "activated" type of hyperthyroidism but there has been an increase in the incidence of occult hyperthyroidism among them which often has been obscured by symptoms attributable to diseases of the cardiovascular, gastro-intestinal, and musculoskeletal systems. The older patient has been unable to respond to increased thyroid hormone production and has not exhibited the usual signs and symptoms of Graves' disease. The disease has progressed insidiously until the patient has been forced to seek medical aid because of such symptoms as extreme weight loss, muscle and joint pain due to weakness, or symptoms of aggravated cardiovascular or gastrointestinal disease or diabetes. Cardiovascular complications most frequently give rise to problems in apathetic hyperthyroidism. In the case of an elderly person with cardiac disease, the possibility of masked hyperthyroidism should be borne in mind. The diagnosis can be established by the serum protein-bound iodine level or by the thyroidal uptake of radioactive iodine. The basal metabolic rate is a reliable indicator if one is aware that a slight to moderate elevation is more significant in an elderly person. A study of 24 elderly patients with thyrotoxicosis showed the most frequent symptoms, in decreasing order, to be: weight loss, cardiac symptoms, weakness, irritability, pressure in the neck, increased cold tolerance, decreased appetite, increased appetite, exophthalmos, diarrhea, and vomiting. The most frequent pertinent findings on physical examination were: palpable thyroid gland, nodular goiter, cardiomegaly, tachycardia greater than 100 per minute, electrocardiographic abnormality, emaciation, apical systolic murmur, pulsations and bruit in the thyroid, fine tremor of the fingers, increased pulse pressure (greater than 90), tracheal compression, and auricular fibrillation. The treatment of choice in approximately half of the patients may be medical. It is considered safe to perform a one-stage subtotal thyroidectomy of both lobes after control has been achieved with antithyroid drugs in carefully selected cases. These patients require meticulous pre- and postoperative care. Those with apathetic thyrotoxicosis tolerate sedation poorly, so preoperative sedation must be very light and local anesthesia should be used. Radioactive iodine is advantageous in some elderly patients, par-

ticularly when there is a large operative risk. Toxic nodular goiters may be treated with radioactive iodine. Usually the adenomatous glands respond poorly to it, and should be removed whenever possible. The insidious onset of hyperthyroidism in elderly persons provides a rationale for "prophylactic" thyroidectomy in the case of nontoxic nodular goiters. The early recognition of thyrotoxicosis in elderly persons is important because it can be corrected with definitive therapy, and potentially fatal complications avoided.

SIGNIFICANCE OF SMALL PLEURAL EFFUSIONS IN CARDIOPULMONARY DISEASE, AND SOME OTHER OBSERVATIONS ON PLEURAL FLUID IN GENERAL.

Cardon, L. *Ann. Int. Med.* **53:** 765 (Oct.) 1960.

A relatively small pleural effusion may precipitate a critical degree of dyspnea and air hunger and even cause death, in the presence of antecedent cardiac and pulmonary disease which already seriously interferes with pulmonary function and causes difficulty in breathing. As little as 500 ml. may be of significance in this regard. This situation occurs most commonly in aged or elderly persons with co-existent congestive heart failure and pulmonary emphysema or fibrosis; but a summation of other pathologic processes in the lungs (such as infarction, pneumonia or atelectasis) in the presence of heart disease or failure may similarly enhance the final asphyxial effect of a small increment of pleural fluid. Recognition followed by mechanical removal of a small pleural effusion by thoracentesis under these circumstances provides great palliative benefit, and is frequently lifesaving. Dogmatic and axiomatic statements that, in all cases, pleural fluid is not to be tapped unless the upper level reaches a certain arbitrary point (such as the angle of the scapula) condemn many patients to needless suffering and death. Diagnosis of a small effusion in the presence of heart failure and emphysema may be difficult. It is based mainly on a high index of suspicion that any degree and extent of impairment of resonance in the lowermost portions of the posterior aspects of the thoracic cage may be due to pleural fluid, and the free use of exploratory puncture, properly performed, to test this suspicion. Chest roentgenograms are frequently misleading and unreliable. Significant amounts of pleural fluid (500 to 1,000 ml.) may not be detected in the postero-anterior view, or may appear merely as "blunting," "obliteration" or "haziness" of the costophrenic angle. The presenting clinical picture is frequently that of acute pulmonary edema, which obscures the diagnosis of pleural fluid, and is relieved only when the pleural fluid is removed by thoracentesis. "Refractory heart failure," and digitalis intoxication due to overmedication, occur commonly because of unrecognized pleural fluid. Violent restlessness (refractory even to massive doses of sedatives and opiates), inexplicable breathlessness, extreme dyspea, and refusal of oxygen therapy by any avenue of administration, are common symptoms of hidden pleural fluid under the circumstances discussed, and are relieved at once by thoracentesis. Mental and cerebral symptoms simulating—and often mistakenly diagnosed as—senile or toxic psychosis may be caused by asphyxia due to pleural fluid, and be relieved only after thoracentesis. Early thoracentesis is indicated when any degree of hydrothorax in cardiac failure is associated with a significant degree of dyspnea. (From author's summary and conclusions.)

"RHEUMATOID ARTHRITIS" WITH NEGATIVE SEROLOGICAL REACTION.

Dixon, A. St. J. *Ann. Rheum. Dis.* **19:** 209 (Sept.) 1960.

Sixty-one of 63 in-patients with severe, active polyarthritis associated with persistently negative results in the sheep-cell agglutination test (S.C.A.T.) for rheumatoid arthritis were followed for 5.4 years. In 12 patients, at follow-up, the S.C.A.T. findings were positive. In all except 2 of these cases the distribution of arthritis was typical of rheumatoid arthritis, and in 6 subcutaneous nodules developed. The course of the arthritis was not different from that seen in 23 patients in whom the arthritis was also typical but in whom the S.C.A.T. findings remained negative. Both mild and severe end-results were observed.

A persistently negative S.C.A.T. result was compatible with typical rheumatoid arthritis of progressive course and fatal outcome. Eleven patients had proven or probable diseases other than rheumatoid arthritis; these included gout, generalized osteoarthritis, psoriatic arthropathy, reticulohistiocytosis, Takayushu's disease, Reiter's disease, and myelomatosis. Eight patients showed persistently negative S.C.A.T. findings and atypical arthritis. The disease in them conformed to no accepted nosology, and these cases may have been examples of undescribed polyarthritic disorders. The evidence for this seemed strongest in 2 middle-aged females with severe and prolonged central and spinal polyarthritis associated with marked constitutional disease, proceeding to complete remission. A reproducible diagnosis of rheumatoid arthritis requires a positive result with the specific sheep-cell agglutination test as well as clinical evidence of polyarthritis. In clinical studies of this disease the results of agglutination tests should be stated, and patients with persistently negative findings should be excluded or separately assessed. (From author's summary.)

PANCREATITIS AND RENAL INSUFFICIENCY.

Freidell, H. V. *Am. J. Gastroenterol.* **34:** 487 (Nov.) 1960.

Three cases are presented in which acute pancreatitis was complicated by renal insufficiency. Irreversible shock developed in all 3 persons while they were receiving therapy for acute tubular necrosis. The cause of shock was not apparent but it was thought to be due to bacterial endotoxins. The patients deteriorated and died despite the use of vasopressor agents, antibiotics, blood transfusions, and steroid therapy. Interpretation of the elevated serum amylase level presented a problem since, in the presence of renal insufficiency, an elevated level of serum amylase or lipase has no diagnostic significance. Under such circumstances the presence of pancreatitis may be suggested by the history and physical examination. Peritoneal aspiration was not helpful in evaluating an elevated amylase level in one of the patients, although it was significant in another. Pertinent literature on pancreatitis, renal failure, and bacteremia as a cause of shock is cited.

TREATMENT OF CEREBROVASCULAR THROMBOSIS WITH FIBRINOLYSIN. PRELIMINARY REPORT.

Herndon, R. M.; Meyer, J. S.; Johnson, J. F., and Landers, J. *Am. J. Cardiol.* **6:** 540 (Aug.) 1960.

Thirteen patients with severe cerebrovascular thrombosis or embolism were given anticoagulants upon admission, and fibrinolysin therapy was started. The bovine fibrinolysin was given in three doses of 20 to 35 Loomis units per kilogram of body weight over a three-hour to six-hour period on three successive days. Eight patients improved, but 5 did not survive. The pathologic findings in 3 of the 5 were those seen in cerebral ischemia due to thrombosis of the cerebral vessels with ischemic infarction. No thrombus was found in 1 patient. A fresh thrombus was seen in the basilar artery of 1 patient, and in the carotid artery of the other. There was no evidence of intracerebral hemorrhage or hemorrhagic infarction. Reactions were noted in 6 patients: ecchymosis, 1; ecchymosis and hematuria, 1; generalized urticaria, 1; temperature elevation, 1; local erythema and tenderness, 1; and severe local tenderness along the vein of injection, 1. Patients tested two to six months following therapy were found to have become sensitive to bovine fibrinolysin. Fibrinogen levels, determined in 3 patients, showed an initial drop followed by a rapid return toward initial levels after completion of fibrinolysin injection. No significant changes were noted in the leukocyte count, hemoglobin level, and the concentrations of fasting blood sugar, plasma urea nitrogen, or serum glutamic oxalacetic transaminase. It is concluded that intravenous bovine fibrinolysin is a feasible means of treating cerebrovascular thrombosis but that the present data are insufficient to permit conclusions concerning the clinical efficacy of this form of therapy.

FATE OF A PATIENT WITH A SO-CALLED "MILD CORONARY."

Likoff, W.; Dreifus, L., and Bender, S. R. Proc. Thirty-third Scientific Session, Am. Heart Assoc., (abstract) *Circulation* **22:** 780 (Oct.) 1960, Part 2.

The ultimate pathophysiologic manifestation of ischemic heart disease is acute myocardial infarction. Prognostic appraisals of those afflicted are difficult. In these evaluations the term "mild" or "good risk" has come into common usage. It refers to patients who suffer an initial infarction with mild subjective reactions and without arrhythmias, congestive failure or shock. The myocardial involvement is presumed to be limited to small noncritical areas. The electrocardiographic abnormalities mainly revert to normal within short intervals. In these patients there is a small initial mortality (5 per cent), and they are believed to suffer the least significant chronic disability and to require the least vigorous therapeutic measures. One hundred "good risk" coronary patients were observed for five years after the initial infarction, for the purpose of examining the foregoing premies. The following observations were made: 1) 54 per cent suffered from disabling coronary insufficiency pain after recovery from the infarction; 2) 48 per cent had recurrent myocardial infarctions on an average of twenty-one months after the initial attack; 3) 82 per cent of those with recurrent infarction were among the group who had persistent insufficiency pain; 4) the recurrent infarction invariably involved the previously afflicted area of the myocardium; and 5) the mortality rate in the recurrence group was 18 per cent. The data appear to negate the category of a mild or good-risk coronary patient, particularly when the pain of coronary insufficiency persists after an initial infarction. They also suggest that in many instances myocardial infarction is produced by an incomplete evolvement of the etiologic factors which then remain poised to re-develop within a short interval. This is a common event in the case of coronary heart disease classified as "mild" or "good risk."

AMYOTROPHIC LATERAL SCLEROSIS: CLINICAL SYNDROME AND DIFFERENTIAL DIAGNOSIS.

Mulder, D. W. *M. Clin. North America* **44:** 1013 (July) 1960.

Amyotrophic lateral sclerosis is a progressive and fatal disease of the motor system characterized by selective involvement of motor neurons. Sensory neurons are not affected, although all anterior-horn cells with the exception of those innervating the muscles subserving movements of the eyes may be destroyed. The disease is insidious in onset, occurs in persons over the age of 30 years, and has its maximal incidence in the fifth and sixth decades. More men than women are affected in a ratio of 2:1. Muscular atrophy with fasciculations, cramping, and weakness commonly mark the onset. Atrophy may commence in any of the striated muscles except for the extrinsic muscles of the eye. Bulbar symptoms occasionally are the presenting complaint, but they usually are associated with termination of the symptoms, death being related to their progression. Hyperactive reflexes, spasticity, and occasionally abnormal plantar responses are seen when the lateral or pyramidal columns are involved. A pseudobulbar type of paralysis occurs when the pyramidal tracts are involved at or above the level of the brain stem. Involvement of the pyramidal tracts may be masked by muscular atrophy and weakness, but invariably is seen at necropsy. Abdominal reflexes remain constant and urinary incontinence is unusual. Although sensory impairment rarely complicates the disease, many older patients have a diminution in vibratory sensation in the lower extremities. Mental symptoms are rare, and emotional incontinence does not often accompany the pseudobulbar palsy. Localized lesions of the cervical portion of the cord and diffuse neuropathy are most commonly confused with amyotrophic lateral sclerosis. Cervical cord lesions are differentiated by the limitation of denervation with resultant atrophy and fasciculation in a few cervical segments. Motor neuronitis, which also may be confused with amyotrophic lateral sclerosis, may be distinguished by the absence of deep reflexes and the presence of sensory findings. The elec-

tromyogram with studies of the nerve after stimulation often assists in diagnosis. The selective pathologic change in this disease suggests that understanding its cause and treatment depend upon better understanding of the physiology of the anterior-horn cell and the differential sparing of motor cells of the third, fourth and sixth cranial nerves. Some variation in the biochemistry of these cells must protect them from this disorder. Further study along these lines will be required in order to provide adequate treatment.

THE BEARING OF PORTAL VEIN CONGESTION ON THE STATE OF THE CIRCULATION IN CIRRHOSIS OF THE LIVER.

Ofstad, J. *Acta med. scandinav.* **168:** 77, 1960, Fasc. 2.

The blood volume and the cardiac index were estimated by the dye dilution technique in 15 patients with cirrhosis of the liver and in 4 patients with thrombosis of the portal vein. The relative blood volume and the cardiac index were lower in thrombosis of the portal vein than in liver cirrhosis, which is an indication that the circulatory changes in cirrhosis arise from damage to the liver parenchyma. The investigation confirms the findings of Murray *et al.* (1958). In thrombosis of the portal vein there was a tendency toward slightly increased blood volumes. Congestion of the portal vein may therefore also play a part in the increase of the blood volume in cirrhosis of the liver. (From author's summary.)

DISTRIBUTION OF SERUM CHOLESTEROL LEVELS AMONG NORMAL MIDDLE AGED MEN.

Pell, S., and Koniecki, W. B. *Delaware M. J.* **32:** 400 (Oct.) 1960.

Serum cholesterol determinations on 1,543 healthy males between the ages of 40 and 64 years showed the mean level to be 243.5 mg. per 100 ml. and the standard deviation 40.5 mg. per 100 ml. The normal range was 164.1 to 322.9 mg. per 100 ml. These results agree with the mean cholesterol levels found in large-scale population studies made in recent years among the healthy adult male population in the United States.

THE LATERAL MEDULLARY (WALLENBERG) SYNDROME: CLINICAL FEATURES AND PROGNOSIS.

Peterman, A. F., and Siekert, R. G. *M. Clin. North America* **44:** 887 (July) 1960.

The Wallenberg syndrome consists of the signs and symptoms resulting from an infarct in the dorsolateral position of the medulla oblongata. Its clinical features are the relatively sudden onset of vertigo, nausea, vomiting, dysphagia, hoarseness, staggering, and incoordination of the limbs on one side of the body. The patient may note headache, pain or numbness on one side of the face, paresthesia of the limbs on the opposite side, and hiccup. Examination shows decrease or loss of pain and temperature sensations on one side of the face, decreased corneal reflex, Horner's syndrome, paresis or paralysis of the muscles of one side of the palate and larynx, weakness of the entire face (peripheral type), and incoordination of the limbs, all on the same side as the lesion. On the opposite side, decrease or loss of pain and temperature sensations are noted. The gait is ataxic. Fine or coarse nystagmus may be seen on gaze to either side, but it occurs more often to the side of the lesion. Muscle stretch reflexes, muscular strength in the limbs, and sensations of light, touch, position and vibration are normal. The syndrome is the result of an infarct in an anatomic area rather than of an occlusion of a specific artery. The lesion affects various structures in the dorsolateral portion of the medulla, and the abnormalities encountered will vary accordingly, as follows: nucleus and spinal tract of the trigeminal nerve (facial and corneal anesthesia); the spinothalamic tract (limb and body anesthesia); inferior cerebellar peduncle (gait and limb ataxia); vestibular nuclei (nausea, vomiting, nystagmus); descending sympathetic fibers (Horner's syndrome); nucleus ambiguus of the vagus nerve (palatal

and laryngeal palsy); and intramedullary fibers of the facial nerve (facial weakness). A study of 35 cases that could be traced showed the onset of the condition was at middle age and later. It was preceded by two to five transient episodes suggestive of ischemia of the brain stem. Hypertension, diabetes mellitus, or cardiac disease frequently was associated with the syndrome. The onset of symptoms was often abrupt. In other instances, symptoms developed over a twelve-hour period, or over twelve hours to three days. The symptoms and clinical abnormalities were those previously listed. Extreme variation occurred in the loss of pain sense and temperature sense over the body and limbs. A complete Horner's syndrome was present only five times, and portions of the syndrome in other cases. Roentgenograms of the skull were normal except for calcification of the carotid arteries in a few instances. Protein concentration in the cerebrospinal fluid, when measured, varied from 30 to 150 mg. per 100 ml., and the numbers of lymphocytes were 1, 3, 6 or 25 per ml. Eight of 10 electroencephalograms were normal or showed minimal, nonspecific generalized dysrhythmia; the other 2 showed focal slow waves over the cerebral hemispheres but no corresponding neurologic abnormalities. The immediate outlook for life in this syndrome is good. The survival rates in the series were. 1 year, 83 per cent; three years, 80 per cent; five years, 59 per cent. Among the causes of death were myocardial infarction, cerebrovascular accident, pneumonia and renal failure. Hypertension and diabetes were present in a high percentage of the patients who died. The effect of age on mortality was not studied because the sample was small. Age, however, seemed to be the determining factor in whether or not the patient was able to work at the time of follow-up. The residual neurologic difficulties were equally severe in both groups. Residual, though minimal, neurologic deficits were noted by the majority of patients for many years.

SPECIFICITY OF PLASMA FIBRINOGEN CHANGES FOR ATHEROSCLEROSIS.

Pilgeram, L. O.; Schram, A. C., and Mills, D. Proc. Thirty-third Scientific Session, Am. Heart Assoc., (abstract) *Circulation* **22:** 796 (Oct.) 1960, Part 2.

A 34 per cent increase in the plasma fibrinogen level was found in patients who had recovered from the trauma of a myocardial infarction or a cerebrovascular accident not less than six months before, and who had not received anticoagulant therapy for at least five months preceding the donation of a blood sample. The interval of time between the myocardial infarction or cerebrovascular accident and analysis indicated 1) that the elevated fibrinogen levels cannot be due to inflammatory conditions or traumatized tissue resulting from the vascular incidents, and 2) that the fibrinogen level does not return to normal following a myocardial infarction or cerebral vascular accident. Occlusion of beta- or low-density lipoproteins in the fibrin coagulum did not account for the elevated levels of fibrinogen, as was shown by experiments in which 1) known quantities of alpha- and beta- lipoproteins were added to the test system; 2) correction was made for the occlusion factor; 3) the increased yield caused by this occlusion factor represented only a 3.5 per cent increase in fibrinogen yield for as much as a 300 per cent increase in the level of beta-lipoproteins. The data indicate that the fibrinogen level not only increases with age but also superimposes upon the arteriosclerotic patient an increase in addition to that occurring with increasing chronologic age. These findings support recent reports on the role of fibrin in vascular hypertrophy and atheromatous development. In view of these data, the merit of securing a physiologic homeostasis of fibrinogen metabolism prior to the onset of myocardial infarction in cerebral accidents appears to be unquestionable.

GOUTY HEART.

Pund, E. E., Jr.; Hawley, R. L.; McGree, H. J., and Blount, S. G., Jr. *New England J. Med.* **263:** 835 (Oct. 27) 1960.

This is the twelfth reported case of gouty involvement of the heart. The patient died seven days after admission. At necropsy, a single, large tophus was found at the base of

the mitral valve that extended through the myocardium into the epicardial fat tissue adjacent to the left circumflex coronary artery. Microscopic deposits of urates were found in the leaflets of the mitral and tricuspid valves. Yellow-white plaques were also observed in the aortic valve. Although there was no history or clinical signs, a recent myocardial infarction was present in the lateral wall of the left ventricle. Generalized atherosclerosis and arteriolar sclerosis were severe. Extensive calcification had occurred in the walls of many small arteries, especially those of the skin, the skeletal muscle of the lower extremities and the kidneys. This calcification differed from that seen in chronic hypertensive cardiovascular disease and may have been related to the chronic gout, representing secondary calcification of tophaceous deposits in the media of these vessels. These changes in the vessels of the skin appeared to be the etiologic basis for peripheral gangrene. Arteriolar nephrosclerosis was extremely severe. Findings consistent with uremic pericarditis were present. Such diffuse myocardial deposits as were found in this case have been described only once before. The presence of extensive gangrene of the skin has not previously been described in gout.

EXPERIENCES WITH CLOT-LYSING AGENTS IN CORONARY THROMBOSIS.

Richter, I. H.; Musacchio, F.; Cliffton, E. E.; Nassar, A.; Kaplan, L.; Favazza, A. G., and Akbari, A. *Am. J. Cardiol.* **6:** 534 (Aug.) 1960.

Fibrinolysin (Thrombolysin) was administered to 60 patients with various thromboembolic diseases, 45 of whom had myocardial infarction. The majority of the patients were between the ages of 50 and 79 years. There were 30 men and 15 women. Associated diseases included hypertension, diabetes, previous myocardial infarction, previous angina, peptic ulcer, previous congestive heart failure, phlebitis, uremia, and anemia. The dosage administered by intravenous drip was approximately 1,000 units per kilogram of body weight per hour for six to eight hours a day for four days. Benadryl was given during therapy and anticoagulants administered commencing a few hours after the last dose of fibrinolysin. Thirty-nine patients survived and 6 patients, who were in a state of shock or congestive heart failure at the time of admission, died—2 of them before adequate dosage could be administered. Permanent relief of precordial pain was achieved in 38 patients within a short time. Seven patients had intermittent precordial pain during and after therapy. No significant regressive changes occurred in the electrocardiogram except for the disappearance of Q waves in lead V_4 in 1 patient. The systolic blood pressure in 4 patients with hypertension fell from 40 to 70 mm. Hg during therapy, without apparent ill effects. Thirty-three patients experienced a significant elevation in temperature during and after therapy. Six patients had minor side-reactions and 4 had significant evidence of bleeding. One patient with rectal bleeding and evidence of uremia and anemia died six days after admission, probably of heart failure and uremia. Whole blood clot lysis was complete in 2 patients in two hours, in 1 patient in twelve hours, and in 1 patient in sixteen hours. The prothrombin times during therapy were as follows in the numbers of patients stated: 18 to 20 seconds, 17; 21 to 25 seconds, 10; 26 to 30 seconds, 5; and 60 seconds, 2. This is regarded as a preliminary report. Patients are being re-evaluated and compared with a control group on a long-term basis.

EFFECTS OF LONG-TERM ADMINISTRATION OF ESTROGENS ON SERUM LIPIDS OF POSTMENOPAUSAL WOMEN.

Robinson, R. W.; Higano, N., and Cohen, W. D. *New England J. Med.* **263:** 828 (Oct. 27) 1960.

One hundred and eight postmenopausal women, the majority of whom had vascular diseases, were treated for one year with estrogens at various dosage levels in an attempt to determine an optimal dose that would produce satisfactory serum lipid changes with few side-effects. A minimal dosage of 0.01 mg. of ethinyl estradiol administered daily to 15

women for one year had no significant effect on the serum levels of total cholesterol and phospholipids, or on the ratio of cholesterol to phospholipids. There was a small but statistically significant decrease in the average ratio of beta-lipoprotein to alpha-lipoprotein cholesterol. No estrogenic side-effects were observed at this low dosage level. Groups of 14 to 21 women were given various dosages of conjugated equine estrogens, ranging from 0.625 to 10 mg. daily for one year. It was found that significant serum lipid changes occurred at all dosage levels, and were maximal at 10 mg. Dosages of 2.5 mg. and higher were accompanied by side-effects in most patients. If an optimal dosage is to be selected for long-term administration, it should be one that produces satisfactory serum lipid changes, with minimal disturbing side-effects. These studies show that 1.25 mg. daily appears to fulfill these requirements in patients with intact uteri. A therapeutic trial of 2.5 mg. is suggested in somen with abnormal patterns of serum lipids who have previously been subjected to hysterectomy. If the lipid abnormalities persist, 5 or 10 mg. of the estrogen preparation daily should be tried. (From authors' summary and conclusions.)

MYASTHENIA AND MALIGNANT INTRATHORACIC TUMOR.

Rooke, E. D.; Eaton, L. M.; Lambert, E. H., and Hodgson, C. H. *M. Clin. North America* **44:** 977 (July) 1960.

A type of muscular weakness is described which has been termed the "myasthenic syndrome sometimes associated with small cell bronchogenic carcinoma." It differs from myasthenia gravis, and a pulmonary neoplasm is present in a substantial proportion of patients affected. Clinically there is weakness and undue fatigability of the proximal muscles of the extremities, temporary increase in the strength of the muscles in response to voluntary exercise of short duration, decrease or absence of muscle-stretch reflexes particularly in the lower extremities, relatively poor response to neostigmine, marked sensitivity to d-tubocurarine, dryness of the mouth, loss of potentia, and the presence of peripheral paresthesias. The syndrome differs from typical myasthenia in that involvement of the proximal girdle musculature predominates, and involvement of the bulbar and ocular musculature is rare; the temporary increase in muscular strength is unusual, and the alteration in the muscle-stretch reflexes is not characteristic of myasthenia gravis. Neither is the response to neostigmine and to d-tubocurarine the same as in myasthenia gravis. Quantitatively, the electromyographic characteristics differ from those of myasthenia gravis. In diagnosis, the most helpful difference is the response to a single maximal stimulus applied to a motor nerve. In myasthenia gravis, a block of neuromuscular transmission may exist in the response of a rested muscle to a single nerve impulse and post-tetanic facilitation of neuromuscular transmission occurs, but these phenomena are marked in the myasthenic syndrome, S. C. Ca (as it is abbreviated). All 19 patients analyzed were above the age of 50 years and most of them above age 60. Group A comprised 7 patients with an abnormal appearance of the chest in the admission roentgenogram. Each had a small-cell carcinoma. In the 7 patients of Group B, the myasthenic syndrome was identified, although examination of the chest yielded negative results; in each, a pulmonary neoplasm subsequently developed. The 5 patients in Group C showed the myasthenic S. C. Ca syndrome but without the development of a pulmonary neoplasm. Treated with cholinergic medications these, and some patients with pulmonary neoplasms, showed a response less satisfactory than that in myasthenia gravis. All of the tumors were small-cell (or oat-cell) carcinomas. Histologically the muscle in 13 patients had a normal appearance five times; in the other 8 cases, mild, scattered, nonspecific degeneration of muscle fibers and occasional focal collections of sarcolemmal nuclei were seen. In 1 case the characteristics of myositis were present. In the only instance in which peripheral nerves were examined histologically, the sciatic and peroneal nerves showed moderately severe demyelination. Posterior root ganglia showed disintegrating nerve cells with proliferation of cap cells, macrophages and swellings, and disintegration of axis cylinders of these cells. No abnormalities were found in the cerebellum and the spinal cord at the cervical, dorsal and lumbar levels. There is as yet no explanation for an apparent relation between a myasthenic syndrome and the presence of a malignant intrathoracic tumor.

MASSIVE HEMORRHAGE FROM DIVERTICULITIS.

Ross, S. T., and Eddy, H. J. *Dis. Colon* **3:** 441 (Sept.–Oct.) 1960.

Contrary to the usual consensus, massive bleeding from a source distal to the ileocecal valve should be considered to be of diverticular origin until evidence showing otherwise is discovered. Massive hemorrhage is considered to be that of a degree sufficient to require hospitalization of the patient or the administration of a transfusion. The major diseases to be ruled out in the differential diagnosis are ulcerative colitis and malignancy. Ulcerative colitis is easily differentiated by its pathologic features, and roentgenographic studies should make diagnosis of carcinoma possible. The thesis that diverticula of the colon should be suspected in massive hemorrhage from the colon is supported by 1) the findings in 5,000 cases in private practice, 2) the records of 45,000 hospital cases, and 3) 20 cases presented here. Among 420 cases of diverticulosis or diverticulitis in Group 1, massive hemorrhage occurred in 9, whereas it occurred in only 1 of 231 cases of malignancy of the colon. Since among the hospitalized patients (Group 2), including 202 with diverticulosis or diverticulitis, diverticular disease was diagnosed only 9 times, it appears that many cases are not being diagnosed but instead are thought to be cases of intestinal hemorrhage or hemorrhage from a peptic ulcer. In support of the belief that diverticula should be suspected as the site of origin of bleeding when diverticula of the colon are present, and to refute the thought that an underlying neoplasm has been missed, the records of the hospital cases showed: 1) freedom for years from further bleeding, 2) no other cause for hemorrhage found at operation, 3) hemorrhage was stopped by removal of a diverticular segment of the colon, 4) no other evidence of disease found in the resected specimens, and 5) no roentgenographic and clinical evidence of gastro-intestinal disease other than diverticula. Among the 20 patients reported (Group 3), 11 were females and 9 were males. The average age was 71.7 years. In each case bleeding was massive, diverticulosis or diverticulitis was seen on x-ray examination, and there was no evidence of peptic ulcer or tumor. Emergency resection was required in 4 instances. The hemoglobin and hematocrit readings agreed roughly, but there was a disparity between these and the blood pressure readings. As for pathogenesis, it is postulated that inflammation of the neck of the diverticulum can cause erosion into an arterial vessel of significant size. When the vessel is inelastic because of arteriosclerotic disease, uncontrollable bleeding may occur.

SIMPLE OFFICE OPERATION FOR SPASTIC ENTROPION.

Rowe, F. A. *J. Tennessee State M. A.* **53:** 436 (Oct.) 1960.

Seven cases of spastic entropion in persons aged 66 to 82 years were operated upon by the technic of Wies (Tr. Am. Acad. Ophthalmol. **59:** 503, 1955). Under procaine anesthesia and with a lid plate protecting the globe, an incision is made 4 mm. below the lid margins and extending approximately the entire length of the lid. It is made perpendicularly through the lid, orbicularis, tarsus and conjunctiva. Then a double armed 4-0 silk is placed centrally into the lower lip of the conjunctiva with the loop inside of the conjunctival surface. Similar sutures are placed medially and laterally to the central suture. The suture ends are brought out through the upper lid of the skin surface and tied over rubber pegs. The skin edges are closed with interrupted sutures of the same material. A pressure patch is applied for five days. The interrupted sutures are removed after five days, and the double armed sutures after seven days. Of 7 patients treated in this manner, entropion was cured in 4, but recurred in four to six months in the other 3.

TREATMENT OF CORONARY INSUFFICIENCY WITH ISOSORBIDE DINITRATE.

Sherber, D. A., and Gelb, I. J. Proc. Thirty-third Scientific Session, Am. Heart Assoc., (abstract) *Circulation* **22:** 809 (Oct.) 1960, Part 2.

Isosorbide dinitrate was evaluated clinically in 40 patients (24 males and 16 females) with coronary insufficiency. The duration of treatment ranged from three to nineteen months. The usual dosage was 10 mg. four times daily. The criteria of activity were de-

creases in the number and severity of anginal attacks. Thirty patients in the group experienced almost complete relief of the anginal syndrome with this medication. Ten experienced a considerable degree of freedom from angina, although they occasionally required some sublingual nitroglycerin. Headache was the only complication with this compound, but the headache was relieved by reduction in dosage and/or salicylates. All patients except 1 were relieved of their angina. Angina recurred after five months of treatment in 1 case. There were no changes in the formed elements of the blood, or in the levels of blood cholesterol and blood sugar during treatment.

ANTICOAGULANT THERAPY IN SYNDROMES OF INTERMITTENT FOCAL CEREBRAL ARTERIAL INSUFFICIENCY: FOLLOW-UP AND COMPARISON OF TREATED AND UNTREATED CASES.

Siekert, R. G.; Millikan, C. H., and Whisnant, J. P. Proc. Thirty-third Scientific Session, Am. Heart Assoc., (abstract) *Circulation* **22:** 811 (Oct.) 1960, Part 2.

During the years 1954–1959, a large group of patients suffering from episodes of focal cerebral arterial insufficiency was treated with anticoagulant therapy. These syndromes of vertebral-basilar and carotid arterial system insufficiency, previously described by the authors, consist of episodes of focal cerebral ischemia lasting fifteen to thirty minutes; the patient is normal between episodes. There were 103 continuously treated patients, and 85 untreated or intermittently treated patients, and they were followed from one to five years. Of patients who received such therapy continuously from the time the diagnosis was established, 85 (83 per cent) remained symptom-free; 5 (5 per cent) continued to have attacks that did not produce cerebral damage; and 7 (7 per cent) suffered a severe stroke. Of the latter group, 4 (4 per cent) died, all from cerebral hemorrhage. The remaining patients died of noncerebral causes. Of the patients who did not receive anticoagulant therapy or who received it only briefly, 36 patients (43 per cent) remained asymptomatic; 15 (18 per cent) continued to have attacks that did not produce cerebral damage, and 30 (36 per cent) suffered a severe stroke. Of the latter group, 9 (11 per cent) died, 2 (2 per cent) from intracerebral hemorrhage. The remaining patients died from noncerebral causes. These results suggest that anticoagulant therapy has a definite place in the treatment of carefully selected patients with intermittent focal cerebral arterial insufficiency.